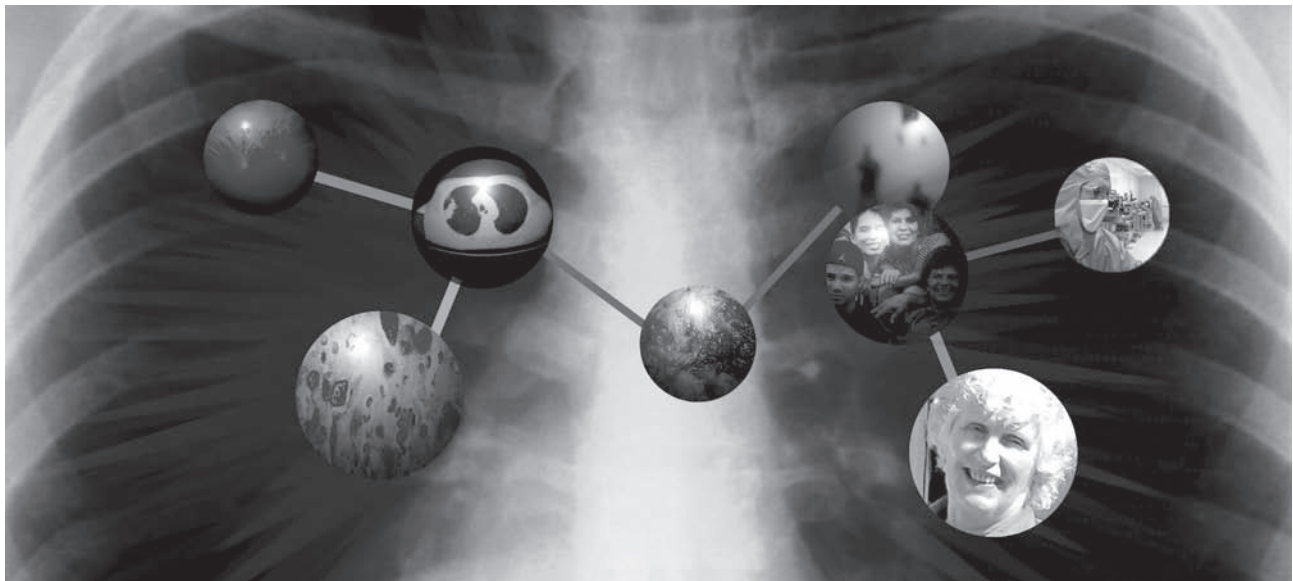


Research Awards Nationwide 2007-2008



ASTHMA

**DISORDERS OF THE LUNG'S BLOOD VESSELS
AND ACUTE LUNG INJURY**

COPD, SMOKING, AND AIR POLLUTION

TUBERCULOSIS

OTHER LUNG INFECTIONS

LUNG CANCER

**THE IMMUNE SYSTEM, INFLAMMATION,
AND LUNG SCARRING**

DISEASES OF INFANTS AND CHILDREN

SLEEP DISORDERED BREATHING

Research Awards Nationwide 2007-08

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*The mission of the
American Lung Association
is to prevent lung disease and
promote lung health.*

INTRODUCTION

The lungs are the doorway to life, providing oxygen and eliminating carbon dioxide. Since they are in constant contact with both the outside air and the body's internal environment, the lungs are uniquely vulnerable to disease. Every year, close to 400,000 Americans die of lung disease, making it the third most frequent cause of death in this country. An additional 35 million of us are living with chronic lung diseases such as asthma and emphysema.

The mission of the American Lung Association is to prevent lung disease and promote lung health through research, advocacy, and education. The American Lung Association Nationwide Research Program supports both the basic and applied sciences related to lung health. Our Asthma Clinical Research Centers Network consists of 20 Centers and a Data Coordinating Center that conduct clinical studies around the country on patients with asthma.

The American Lung Association supports basic and clinical research through training and "seed" grants for beginning investigators, which play a critical role in attracting and retaining talented scientists focused on lung research. Research is the key that will unlock the door to a better tomorrow for all people with lung disease.

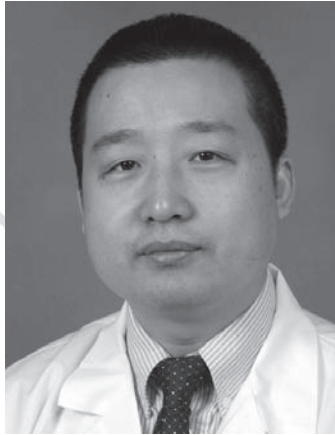
ASTHMA

Close to 22.9 million Americans have asthma, and 12.4 million of them have had an asthma attack in the past year. Asthma is the leading serious chronic illness in children. Although rates have stabilized recently, medical professionals continue to be concerned with the dramatic increase in the number of asthma sufferers over the past two decades, during which asthma prevalence has almost doubled. The enormous impact on the health and well-being of those who are afflicted and the great cost of health care related to asthma are increasingly serious concerns, as is the fact that asthma kills approximately 4,000 Americans each year.

There is reason for optimism despite these bleak facts. Research on asthma offers a real chance for dramatic success, as it is to a great extent a reversible disease. The American Lung Association supports extensive research in asthma in a number of critical areas. Because asthma often runs in families and affects the various races differently, investigators are studying the genes associated with the disease. Cellular and molecular mechanisms of the allergic and inflammatory responses involved in asthma are being studied. New asthma treatments are being examined, and promising new methods for managing the disease especially in emergency rooms and inner city populations, are being sought.

The American Lung Association's Asthma Clinical Research Centers Network is also conducting a number of studies, ranging from investigations into the genetic basis of asthma to examinations of the role of heartburn in precipitating asthma. Other network projects are evaluating the effectiveness of educational programs in controlling asthma.

American Lung Association Scholar: Asthma



QIHAI (DAVID) GU, MD
University of Kentucky

Qihai Gu, MD, knows how much of a difference a grant makes early in a young scientist's career. Dr. Gu, who is Research Assistant Professor of Physiology at the University of Kentucky in Lexington, received a Biomedical Research Grant from the American Lung Association for his project, "Protease-Activated Receptor-2 and Pulmonary C-Neuron Hypersensitivity," in 2006. He is hopeful that the research that he has been able to do using funds from this grant will enable him to receive larger grants from the National Institutes of Health in the future. "I cannot thank the Lung Association enough," he says.

Dr. Gu is in the second year of his grant to study a receptor called protease-activated receptor-2 (PAR2) that contributes to airway inflammation and hyper-responsiveness, or "twitchiness," that is seen in asthma and chronic obstructive pulmonary disease.

"We are uncovering how this receptor acts in the airways and may contribute to airway inflammation," Dr. Gu says. "This may provide valuable information for new therapies to treat airway diseases such as asthma."

To see a complete description of Dr. Gu's research project, please go to page 52.

CHRISTOPHER EVANS, PhD

University of Texas MD Anderson Cancer Center, Houston, TX
Biomedical Research Grant • Co-funded by the American Lung Association and Asociación Puertorriqueña del Pulmón with Support from the American Lung Association of New England

Understanding Role Of Mucus Secretion In The Lungs

Role Of Muc5ac In Airway Homeostasis And Pathophysiology. Under healthy conditions, the airway surface is lined with a thin protective layer of secreted mucus. For people without chronic lung disease, suffering through an upper or lower respiratory tract infection that results in excessive mucus secretion is a nuisance. However, for people with asthma, chronic obstructive pulmonary disease, and cystic fibrosis, this so-called mucus hypersecretion is much more than just an annoyance. It appears, in fact, to play a pivotal role in determining the risk of death during an exacerbation of any of these diseases. Much is unknown about the positive and negative roles of mucus in these diseases. The researchers will test the influence of mucus secretion on airway obstruction by examining what happens when its key components are added in or taken away from the lung. They hope to identify potentially useful therapeutic targets that will help people with chronic lung disease.

JONATHAN FELDMAN, PhD

Ferkauf Graduate School of Psychology
 Albert Einstein College of Medicine, Bronx, NY
Social Behavioral Research Grant • Funded by the American Lung Association with Support from the American Lung Association of New England

Why Do Puerto Rican And African-American Children Have Poorer Asthma Outcomes?

Pediatric Asthma: Disparities And Family Factors. Puerto Rican and African-American children are more likely than Caucasian children to have asthma, and to have worse outcomes related to their asthma, including greater emergency health care use and higher death rates. The researchers will examine racial/ethnic differences in family factors that may contribute to these differences in asthma outcomes. Participants will include Puerto Rican, African-American, and Caucasian children with asthma aged 7-15 and their primary caregivers. This study will measure children's ability to detect when they are having symptoms of asthma at home and at school. This research will also examine when children decide to use their as-needed asthma medication based on their level of lung function. Parents' reports

of their own physical symptoms and their health beliefs about themselves and their child will be assessed in relation to the child's ability to detect asthma symptoms. The role of socioeconomic status and cultural factors will also be measured. This work has important implications for identifying factors that may contribute to poorer asthma outcomes among Puerto Rican and African-American children. The long-term goal of this research is to develop culturally sensitive interventions to improve the management of asthma.

MONICA FOOTE, PhD

Cornell University, Ithaca, NY
Senior Research Training Fellowship • Funded by the American Lung Association

Understanding Immune Helper Cells May Lead To Better Treatment For Allergic Asthma

Epigenetic Regulation Of The Neonatal Th2 Bias. Allergic diseases, including asthma, are inflammatory disorders that result when the immune system mounts an irregular response to environmental allergens. It is estimated that half of Americans with asthma suffer from allergic asthma, a condition that is commonly believed to originate in neonatal or fetal life. Certain white blood cells, called T helper (Th) cells, help other immune cells to mount responses by producing and secreting immune growth factors called cytokines. The immune system produces Th1 and Th2 cells, and both are needed for an effective immune response. People susceptible to allergic asthma, however, often mount potent Th2 responses. The researchers will investigate the mechanisms governing the development and persistence of early-life Th2 function, which will provide information that will be valuable in developing targeted, safe, and effective treatments for allergic asthma in children.

PEISONG GAO, MD, PhD

Johns Hopkins University, Baltimore, MD
Research Grant • Funded by the American Lung Association of the Atlantic Coast

Searching For Asthma Genes In African Americans

Identification Of Asthma Susceptibility Genes On Chromosome 11q In An African-American Population. Asthma is a complex illness with a strong genetic component. Despite an extensive search for genes that make people susceptible to developing asthma, such genes in diverse populations have not

yet been found. Relatively few genetic studies have focused on populations of African descent, a unique population with more severe asthma. The researchers have used a new technology that has provided evidence for asthma genes in five subregions on chromosome 11 in the African-American population. The researchers hope to refine these five subregions and search for genetic variants with the strongest evidence of association with asthma in 1,000 African-American subjects. The identification of genetic variants and genes associated with asthma will contribute to a better understanding of the molecular cause of asthma as well as facilitate the genetic analysis of asthma. This in turn will unlock possibilities for improved early diagnosis and novel therapies.

TEAL HALLSTRAND, MD, MPH

University of Washington, Seattle, WA
Career Investigator Award • Co-funded by the American Lung Association and the American Lung Association of the Northwest

Does Injury To Surface Airway Cells Lead To Exercise-Induced Bronchoconstriction?

Epithelial Basis Of Exercise-Induced Bronchoconstriction. Exercise-induced bronchoconstriction (EIB) is a disorder that causes wheezing and shortness of breath following a short period of exercise. This disorder commonly occurs in people with asthma, as well as athletes and people with nasal allergies who do not have other symptoms of asthma. The researchers hope to determine if injury to the cells that line the surface of the airways causes susceptibility to EIB. They will take small samples of the airway lining cells from asthmatics who have EIB, and compare them with samples from asthmatics who do not have EIB, as well as non-asthmatic individuals. The study will lead to a better understanding of the cause of EIB, which may lead to new therapies to treat this common disorder.

CHRISTY HOULE, MPH

University of Michigan, Ann Arbor, MI
Lung Health Dissertation Grant • Funded by the American Lung Association

Why Do Teens and Parents Answer Questions About Asthma Differently?

Asking Teens And Parents About Asthma.

Management of asthma by adolescents, particularly in urban minority populations, is not well understood. Self-reported asthma information from patients and

families is important to doctors who treat patients and researchers who study the disease. Emerging evidence suggests that adolescents and caregivers give different responses when asked about the teen's asthma, yet there are many unanswered questions about why this is so. This lack of knowledge makes it difficult to develop strategies that may increase the usefulness of self-reported asthma information. Through a series of one-on-one interviews with African-American parents and teens, the researchers hope to identify ways to frame asthma-related questions to this population in order to generate more complete information. This research may lead to refinements in existing approaches to asking questions about asthma in populations that bear a disproportionate burden of the disease.

CLAUDE JOURDAN-LE SAUX, PhD

University of Hawaii, Honolulu, HI
Research Grant • Funded by the American Lung Association of the Mountain Pacific

Role Of Genes In Airway Remodeling In Asthma

Transcriptional Regulation Of Caveolin-1 And -2 In Human Lung Fibroblasts. Asthma represents a chronic inflammatory process of the airways, usually followed by healing. In some patients, however, healing does not occur. The result instead is called airway remodeling. Airway remodeling involves deposits of fibrosis, or scarring, in the airways. To control the fibrotic deposits in the airway, the researchers will identify inflammatory factors that suppress the expression of caveolin genes. These genes are thought to prevent airway remodeling. The researchers hope the information gained in this study will help to develop new therapeutic strategies to stop the progression from airway inflammation to airway remodeling.

IAN LEWKOWICH, PhD

Children's Hospital Medical Center, Cincinnati, OH
Senior Research Training Fellowship • Co-funded by the American Lung Association and the American Lung Association of the Midland States

Why Do Regulatory T-Cells Not Work In People With Allergic Asthma?

The Role of Regulatory T-Cell and Dendritic Cell Interactions In Susceptibility To Allergic Asthma.

This research will examine the role that a specific cell, a regulatory T-cell, or TReg, plays in preventing allergic asthma. TRegs normally help control immune system responses before they become damaging. The

researchers have found that mice that are susceptible to the development of asthma have many TRegs, but these TRegs do not function like those in mice without asthma. They hope to find out whether the mice with asthma are not producing some substance needed to turn off the responses that cause asthma, whether the TRegs in asthmatic mice are normal, but other cells simply fail to see them, or a combination of the two. Once they identify factors that prevent the development of immune system responses that lead to asthma, the researchers hope to use these factors to develop a treatment for allergic disease that reverses the excessive responses that cause asthma.

QING-HUA LIU, MD, PhD

Albany Medical College, Albany, NY

Biomedical Research Grant • Funded by the American Lung Association

Increased Calcium Levels In Cells May Hold Clue To Airway “Twitchiness” In Asthma

Increased Local Ca²⁺ Signaling In Asthmatic Airway Smooth Muscle. Cold air, exercise, and other stimuli can result in wheezing and breathlessness in people with asthma. This is because airways narrow too easily and too much in response to these stimuli, a reaction called airway hyperresponsiveness (AHR), or “twitchiness” of the airways. AHR results from airway muscle cell contraction. This contraction requires an increase in calcium in the cells, which is normally low. However, when the calcium concentration increases to a certain threshold, it will trigger cell contraction. The researchers will study the role of increased calcium in airway hyperresponsiveness. A better understanding of these underlying molecular mechanisms has the potential to improve treatment of asthma.

SAMIR MAKANI, MD

University of California, San Diego, San Diego, CA

Junior Research Training Fellowship • Funded by the American Lung Association of California

Understanding The Immune System’s Role In Asthma

The Role Of Toll-Like Receptor 2 In Allergic Inflammation. The immune system plays an important role in asthma, but much of its function in asthma is still not understood. The immune system has two major parts, the innate immune system and the adaptive immune system. The innate immune system is our first line of defense against invading organisms while the adaptive immune system acts as a second line of defense

and also affords protection against re-exposure to the same pathogen. Recent data suggests the importance of the innate immune response in allergic inflammation. The researchers will study the innate immune system’s role in asthma, focusing on toll-like receptors (TLRs), located on cells of the innate immune system. The researchers hope to provide information that can be used to develop new therapeutic targets for asthma that prevent or modify the initial steps that lead to the cascade of events that end in an asthma attack.

TERUMI MIDORO-HORIUTI, MD, PhD

University of Texas Medical Branch, Galveston, TX

Biomedical Research Grant • Co-funded by the American Lung Association and the American Lung Association of New England

Stopping Allergic Reaction To Cedar Pollen Before It Starts

Structure And Function Of Allergens In Asthma Pathogenesis. Many patients with seasonal allergies suffer increased symptoms and decreased quality of life during pollen season. Allergies can be particularly distressing for people with asthma. An allergy to cedar is one of the most common causes of seasonal allergic diseases in numerous regions around the world. The researchers are studying a type of cedar pollen allergen, looking at sites on the allergen where antibodies bind when they are sent by the body’s immune system in response to the pollen invaders. The antibodies cause certain cells in the body to release chemicals into the bloodstream that cause symptoms of an allergic reaction – runny nose, sneezing, itchy eyes. From this research the scientists hope to identify characteristics that are common to the binding sites of other allergens that are involved in asthma and other allergic diseases. Knowing these characteristics may help them identify additional proteins that have the potential to cause allergic diseases. They also hope to learn how to block the binding of antibodies to the allergen and the cellular events that are responsible for allergic disease in patients. This knowledge would be useful in the treatment of pollen allergies.

TIMOTHY ORISS, PhD

University of Pittsburgh, Pittsburgh, PA
Biomedical Research Grant • Funded by the American Lung Association

Can A Drug That Combats Inflammation In Diabetes Help People With Allergic Asthma?

Effects Of PPAR-gamma On Lung Dendritic Cell Maturation And Migration. In people with allergic asthma, certain types of allergens can trigger asthma attacks and symptoms such as coughing, wheezing, and shortness of breath. Non-allergic individuals do not have an immune system reaction to things they encounter every day in their diet or the air they breathe, a state known as immunologic tolerance. Allergy occurs when tolerance breaks down and an inflammatory response occurs to these common substances. Many people tend to “grow out of” their allergies, suggesting that tolerance has been re-established since these people presumably are still exposed to the environmental triggers that prompted the inflammatory response leading to allergic asthma in the first place. The researchers seek to understand how tolerance is established and maintained by the immune system, and to explore ways to re-establish or initiate tolerance in people where it has failed. The researchers will study one of a class of compounds that has shown effectiveness as an anti-inflammatory agent in the treatment of diabetes, and shows initial promise in the treatment of asthma-like conditions. This research might lead to the future use of these drugs to re-establish immunologic tolerance and thus to effect a “cure” for certain types of asthma.

MAMTA REDDY, MD

Bronx-Lebanon Hospital Center, New York, NY
Research Grant • Funded by the American Lung Association of the City of New York

Two-Pronged Approach To Fighting Asthma In Inner-City Children

The Effect Of Integrated Pest Management On Missed School Days And Quality Of Life In Inner-City Children With Asthma. Asthma is the leading cause of school absenteeism due to a chronic disease. School absenteeism due to asthma is an especially significant problem in the inner-city population. Recent studies have found a strong association between the presence of cockroaches and increases in the severity of asthma symptoms in individuals who are sensitive to cockroach allergens. Unfortunately, the pesticides used to eradicate these culprits can themselves be a direct trigger of asthma symptoms. In addition, children are most sensitive to the toxic effects of pesticides. Therefore, urban

children who suffer from asthma in greater proportions also experience a greater risk of harm from these toxins. Integrated Pest Management is a system that offers safer strategies to battle infestations in addition to the use of non-chemical tools and least-toxic pesticides. The researchers will study whether the effect of home-based Integrated Pest Management in conjunction with comprehensive school-based asthma education will improve school absenteeism rates due to asthma, providing inner-city children with asthma a better opportunity to excel in school.

JULIE B. SEDGWICK, PhD

University of Wisconsin, Madison, Madison, WI
Research Grant • Funded by the American Lung Association of the Upper Midwest

Pinpointing Role Of Eosinophils In The Airways Can Further Understanding Of Asthma

Mechanism Of Urokinase Plasminogen Activator Activation Of Airway Eosinophil Function In Asthma. While a great deal has been learned about the mechanisms of asthma, there are still many poorly understood aspects of this lung disease. Eosinophils are potentially destructive cells that promote airway inflammation in asthma, but the mechanism by which they invade the airways of asthmatics and become activated has not been well defined. The researchers will look at how eosinophils are affected by substances called urokinase plasminogen activator receptors (uPAR), and study the role of increased eosinophils in the airways of people with allergic disease and asthma. This information will be critical to therapeutic strategies aimed at this cell.

MARION SILLS, MD

University of Colorado, Denver, CO
Social Behavioral Research Grant • Funded by the American Lung Association

Helping Emergency Departments Give Children With Asthma Attacks Timely Care

The Association Between Emergency Department Resources And Pediatric Asthma-Related Quality Indicators. Children with asthma attacks recover more quickly if they get timely emergency department (ED) treatment. The researchers will examine the importance of timeliness of treatment for children with acute asthma attacks, both in terms of what factors may contribute to improved timeliness and how children benefit from improved timeliness. The factors that improve timeliness in other medical conditions, like heart at-

tacks, are related to the resources available in the ED and the demands being placed on those resources. If the ED does not have enough nurses, doctors, beds or other resources to accommodate the patients arriving, the ED is said to be “overcrowded.” Patients with heart attacks have to wait longer for treatment if they are in an overcrowded ED, and delaying the care of heart attacks lowers a patient’s chances of a good recovery. By figuring out which components of ED resources are most important for timeliness of asthma care, the researchers can help ED administrators and providers better understand how to give children more timely care for asthma attacks.

OMAR TLIBA, DVM, PhD

University of Pennsylvania, Philadelphia, PA
Biomedical Research Grant • Funded by the American Lung Association

Investigating Causes Of Steroid-Resistant Asthma May Lead To New Treatments

Mechanisms Of Steroid Resistance In Airway Smooth Muscle Cells. Although most people with asthma respond to treatment with corticosteroids, these drugs don’t work in a substantial number of patients. Despite treatment with high doses of corticosteroids, these patients still have persistent lung inflammation and labored breathing, and are at increased risk of dying from asthma attacks. Advances in understanding the mechanisms that are involved in the diminished action of corticosteroid actions will lead to the development of more effective therapy for patients who do not respond to steroids. The researchers will study airway smooth muscle, a lung tissue that plays a key role in airway inflammation and bronchial hyperresponsiveness (airway “twitchiness”), two main features of asthma. They hypothesized that chemical messengers called cytokines, which are released by immune cells in response to asthma triggers such as allergens and viruses, reduce the actions of corticosteroids in airway smooth muscle. The researchers will examine how these cytokines interfere with the responsiveness of airway smooth muscle cells to steroids. This research may offer insight into the design of new treatments for steroid-resistant asthma.

WENWU ZHANG, PhD

Indiana University, Indianapolis, IN
Senior Research Training Fellowship • Funded by the American Lung Association

Investigating How Airway Smooth Muscle Contracts In Asthma

Cytoskeletal Mechanisms For The Regulation Of Airway Smooth Muscle Function. In people with asthma, airway smooth muscle is excessively sensitive to various stimuli and contracts, narrowing the airways, and causing airflow obstruction. The molecular mechanisms by which airway smooth muscle responds to external forces and regulates its contractions are not known. The researchers will study the way in which mechanical forces on the lung that are present during breathing affect the responsiveness of the airway muscle. This research may provide a basis for the development of new therapeutic approaches for the treatment of asthma.

Asthma Clinical Research Centers: A Unique Network To Benefit Patients

The Asthma Clinical Research Centers (ACRC) Network, sponsored by the American Lung Association, conducts large clinical trials that provide vital information about caring for people who have asthma. The Network comprises 20 clinical centers and a data coordinating center, making it the largest of its kind. Its unique focus on large numbers of patients differentiates it from current federally funded and commercial research, and provides practical information about asthma care that has direct benefits for patients. The ACRC Network is currently conducting the following studies:

ASTHMA AND ACID REFLUX DISEASE: TREATING ONE CONDITION CAN RELIEVE THE OTHER

SARA: Study of Acid Reflux and Asthma

Funded by the National Institutes of Health's National Heart, Lung, and Blood Institute

Acid reflux disease, also known as gastroesophageal reflux disease or GERD, is frequent among people with poorly controlled asthma. It often occurs with no symptoms and can induce constriction of the airways. Poorly controlled asthma patients are frequently treated for GERD with drugs that suppress gastric acid, but this approach is expensive and its benefit has not been established. This clinical trial is testing the hypothesis that treating GERD with a class of drugs called proton pump inhibitors will reduce the frequency of exacerbations (worsening of the problem) in people with inadequately controlled asthma. Four hundred people between the ages of 18 and 60 who have asthma that is not well controlled with inhaled steroids are being studied, and are randomly assigned to treatment with either a proton pump inhibitor or a placebo. The results will point the way to more effective methods to control acid reflux and prevent it from contributing to asthma.

CHILDHOOD ASTHMA AND ACID REFLUX DISEASE: TREATING ONE CONDITION CAN RELIEVE THE OTHER

SARCA: Study of Acid Reflux and Childhood Asthma

Funded by the National Institutes of Health's National Heart, Lung and Blood Institute

Acid reflux disease, also known as gastroesophageal reflux disease or GERD, is frequent among people with poorly controlled asthma. It often occurs with no symptoms and can induce constriction of the airways. Poorly controlled asthma patients are frequently treated for GERD with drugs that suppress gastric acid, but this approach is expensive and its benefit has not been established. This clinical trial is testing the hypothesis that children with symptomatic asthma have improved asthma control when treated for gastroesophageal reflux disease with a class of drugs called proton pump inhibitors. Three hundred children between the ages of 6 and 17 who have asthma that is not well controlled with inhaled steroids are being studied, and are randomly assigned to treatment with either a proton pump inhibitor or a placebo. The results will point the way to more effective methods to control acid reflux and prevent it from contributing to asthma.

Asthma Clinical Research Centers (ACRC) Participants

LYNN GERALD, PhD

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DISORDERS OF THE LUNG'S BLOOD VESSELS AND ACUTE LUNG INJURY

Acute lung injury, also known as ARDS, is a syndrome in which the small blood vessels in the lungs become widely impaired, causing them to leak fluid and inflammatory cells into the lungs as a response to infection, shock, or the presence of noxious agents. Approximately 150,000 Americans are affected with ARDS each year, and it is often the major complication of extensive infection, surgery, trauma, chemotherapy, and lung transplantation. No effective treatment yet exists.

Pulmonary arterial hypertension is a condition in which the blood vessels in the lungs constrict abnormally, forcing the heart to work harder to propel blood through the lungs and causing the blood pressure within the lungs to rise. It occurs in response to a variety of associated disorders, ingestion of certain medications, and also in an “idiopathic” form that is without a known cause.

American Lung Association researchers are attacking the problem of ARDS primarily on the cellular and molecular levels. Researchers are discovering new chemical pathways which mediate this devastating disease and are using this information to develop novel methods for treatment and prevention. The mechanisms of pulmonary hypertension are being studied from several perspectives as well. Here, too, the emphasis is upon understanding basic mechanism so that new therapeutic approaches can be tried. Novel ideas abound, such as using medications related to Viagra® to treat this condition.

Finally, to clarify how water movement across the lungs is regulated, basic studies are exploring the role of the lung membranes in transporting water and salts. Such studies are critical in understanding the mechanisms of and developing treatments for pulmonary edema and pulmonary arterial hypertension.

American Lung Association Scholars: Disorders of the Lung's Blood Vessels



LAURA FREDENBURGH, MD
Brigham and Women's Hospital

Laura Fredenburgh, MD, has been investigating the effects that the enzyme cyclooxygenase-2 (COX-2) has on the development of pulmonary hypertension with the support of a research grant from the American Lung Association. COX-2 is the enzyme targeted by drugs known as COX-2 inhibitors, and plays a central role in many inflammatory disease processes.

“So far, we have learned that COX-2 deficiency is detrimental during exposure to hypoxia (low oxygen levels) and leads to very severe pulmonary hypertension,” Dr. Fredenburgh says. She has found that smooth muscle cells lining pulmonary arteries deficient in COX-2 contract more after exposure to low oxygen levels, and that the lack of COX-2 appears to be responsible for this effect. “If we add back two particular compounds made by COX-2 to pulmonary artery smooth muscle cells, we can reverse this effect,” Dr. Fredenburgh says. Her findings raise the possibility that COX-2 inhibitors might worsen symptoms in patients with pulmonary hypertension.

“We hope that this research will lead to novel therapies with the potential to reverse pulmonary vascular remodeling and halt progression of this incurable disease,” Dr. Fredenburgh says.

“American Lung Association funding through receipt of the Biomedical Research Grant has been invaluable to me at this time in my career, as I am in a critical transition toward becoming an independent investigator,” she says. “The publications that will result from my American Lung Association-funded research will help me succeed in my goals of becoming an independent physician-scientist. By the completion of this proposal, I will be well positioned to submit a competitive NIH R01 application.”



LAURA GONZALEZ BOSCO, PhD
University of New Mexico

Laura Gonzalez Bosc, PhD, is studying the underlying mechanisms that cause pulmonary arterial hypertension (PAH), a chronic and disabling lung condition in which the blood pressure in the lungs is abnormally high.

With the help of an American Lung Association research grant, Dr. Gonzalez Bosc is looking at how a particular transcription factor, a protein that controls gene expression (the process by which the information in a gene translates to proteins) is activated in the lungs' blood vessels when they are deprived of enough oxygen. This transcription factor, called NFAT, is involved in changes in the blood vessel walls, called vascular remodeling, that lead to PAH. In the study, the researchers are simulating the lack of oxygen that occurs in people living at elevated altitudes or in patients with chronic obstructive pulmonary disease.

The NFAT transcription factor she is studying, may provide valuable information about how pulmonary hypertension develops. “If we establish the mechanisms of NFAT, we might be able to modify its activity, and use it in a therapeutic way to treat or prevent the development of pulmonary hypertension,” she says.

To see a complete description of Dr. Fredenburgh's research project, please go to page 19.

To see a complete description of Dr. Gonzalez Bosc's research project, please go to page 19.

WILLIAM ALTEMEIER, MD

University of Washington, Seattle, WA

Biomedical Research Grant • Support of this grant comes from the Mary Fuller Russell Research Fund

Studying Protein's Role In Acute Lung Injury

Fas-Induced Inflammation: Mechanisms And Role In Acute Lung Injury. Acute lung injury remains a cause of illness and death in the intensive care unit. Despite extensive research efforts, the mechanisms involved in the development of acute lung injury are still not completely understood. Research studies on humans and animal models have identified activation of a protein named Fas as a potentially important mechanism in the development of lung injury and inflammation. The researchers will study the mechanism by which Fas causes inflammation and evaluate the role of inflammation in Fas-induced lung injury. The results of this research will provide new insight into how Fas activation contributes to the development of acute lung injury. This will in turn guide future efforts to develop novel therapies effective in preventing acute lung injury.

KONSTANTIN BIRUKOV, MD, PhD

University of Chicago, Chicago, IL

Career Investigator Award • Co-Funded by the American Lung Association and the American Lung Association of the Upper Midwest

Can A Drug Used To Protect Against Radiation Damage Also Treat Lung Injury?

Novel Strategies For Treatment Of Acute Lung Injury Using Radiation Protector Amifostine. Acute lung injury (ALI) and the more severe respiratory distress syndrome (ARDS) are types of severe, acute lung dysfunction affecting all or most of both lungs that occurs as a result of illness or injury. ARDS has a case fatality rate of 30-40%. Despite recent progress in treatment of acute lung injury, there is still no satisfactory strategy to reduce lung damage and tissue injury in this condition. The researchers will study the compound amifostine, a drug used to control some side effects of chemotherapy and radiation therapy, to see whether it can significantly reduce acute lung injury induced by infectious agents. Amifostine belongs to a group of agents called cytoprotectants, which protect normal tissue from some of the side effects caused by some treatments for cancer. The researchers believe that studying amifostine's protective effects may bring a promising direction in drug discovery aimed at the development of new drugs for prevention of pulmonary edema (fluid in the lungs) as a result of acute lung inflammation and trauma.

ANNA BIRUKOVA, MD

University of Chicago, Chicago, IL

Biomedical Research Grant • Co-funded by the American Lung Association and the American Lung Association of the Upper Midwest

Growth Factor May Play Role In Treating Acute Lung Injury

Cell Adhesions In Hepatocyte Growth Factor-Induced Lung Endothelial Barrier Protection. Acute respiratory distress syndrome (ARDS) remains a major cause of illness and death. During the acute phase of lung injury, protein-rich fluid can flow into the spaces between the air sacs in the lung, causing pulmonary edema, or fluid in the lungs. A protein called hepatocyte growth factor (HGF) is one substance that appears in the lung after acute lung injury, and regulates a wide variety of events. Recent studies have suggested an important role of HGF in protecting against this fluid leak in the lungs. The researchers will study whether HGF can play a key part in significantly reducing the acute phase of ARDS associated with increased fluid leak in the lungs. If so, the findings would suggest a potential role for HGF in treating acute lung injury.

YUANNING CAO, PhD

Johns Hopkins University, Baltimore, MD

Research Training Fellowship • Funded by the American Lung Association of the Atlantic Coast

Insights Into Protein Family Involved In Pulmonary Hypertension May Lead To Treatments

Calcineurin/NFAT-Dependent Regulation Of TRPC Channels In Pulmonary Hypertensive Rats. Pulmonary arterial hypertension (PAH), abnormally high blood pressure in the arteries of the lungs, can progress to heart failure and death. Current therapies for PAH are limited. Recent research has shown that pulmonary hypertension is associated with changes in smooth muscle cells of pulmonary arteries. Increasing calcium inside these cells leads to pulmonary artery contraction and promotes overgrowth of these cells, which narrows the inside of the arteries, leaving less room for blood to flow through. The researchers will study how certain genes are "turned on" during the process of pulmonary hypertension development. They will focus on the interactions between two families of proteins called TRPC and NFAT, which have been shown to play important roles in regulating various functions of smooth muscle cells in blood vessels. The research will provide important information on mechanisms that contribute to the development of pulmonary hypertension. This information may lead to the development of novel therapeutic treatment for this deadly disease.

SERGEI DANILOV, MD, PhD

University of Illinois, Chicago, Chicago, IL

Career Investigator Award • Co-funded by the American Lung Association and the American Lung Association of the Upper Midwest

Uncovering Enzyme's Role In Pulmonary Hypertension

Role Of Caveolin-1 In Lung Endothelial ACE Expression. Pulmonary hypertension, or high blood pressure affecting the pulmonary blood vessels, is difficult to treat and is usually fatal within a few years of diagnosis. The cells that make up the inside layer of the lung blood vessels, called dysfunctional pulmonary endothelium, have a central role in the initiation and progression of severe pulmonary hypertension. The researchers previously have shown that an enzyme called angiotensin-1-converting enzyme (ACE), which is involved in the regulation of blood pressure, plays a role in the development of pulmonary hypertension. They will study abnormalities in structures called caveolae that are found in endothelial cells, to see if they affect ACE production and function in lung blood vessels. The researchers believe that better understanding the mechanisms that govern production of ACE in the lung will greatly enhance the understanding of the development of pulmonary hypertension and facilitate the development of new, effective treatments of this severe lung disease.

VINICIO DE JESUS PEREZ, MD

Stanford University, Palo Alto, CA

Senior Research Training Fellowship • Funded by the American Lung Association

Chemical Pathways May Hold Key To Pulmonary Arterial Hypertension

Cross-Talk Between The Wingless And Bone Morphogenetic Protein Signaling Pathways In Pulmonary Artery Endothelial Cells. Pulmonary arterial hypertension (PAH) is a rare but devastating disorder characterized by elevated pressures in lung blood vessels. Without treatment, PAH can progress to heart failure and death. While the cause of PAH is not known, it is thought that the disease may start when pulmonary blood vessels are injured, and in response cells multiply out of control, leading to blocking of small blood vessels. Mutations in a chemical signaling pathway called bone morphogenetic protein (BMP) are known to contribute to the disease's development, but other factors may also play critical roles in disease development and progression. The researchers will study how BMP interacts with another chemical pathway called

the wingless (Wnt) pathway, which plays a crucial role in regulating key cellular processes. They will see how BMP and Wnt impact growth, survival, and migration of cells, critical processes that are abnormal in PAH. Understanding how these two pathways interact may increase the knowledge of how PAH develops and also may reveal potential targets for future therapies to help improve the care of patients with this devastating disease.

HUI DONG, MD, PhD

University of California, San Diego, San Diego, CA

Research Grant • Funded by the American Lung Association of California

Searching For Answers To Mystery Of Idiopathic Pulmonary Arterial Hypertension

Role Of Na/Ca Exchange In The Pathogenesis Of Idiopathic Pulmonary Arterial Hypertension. In pulmonary arterial hypertension (PAH), the muscles within the walls of pulmonary arteries tighten up and the walls of the arteries thicken as the amount of muscle increases (overgrows) in some arteries. This narrows the inside of the arteries, leaving less room for blood to flow through. The result is that the right side of the heart works harder to pump blood through the lungs. Over time, the heart muscle weakens and loses its ability to pump enough blood. This is called right heart failure, which is the most common cause of death in people with PAH. One type of PAH is called idiopathic pulmonary hypertension (IPAH), in which PAH is inherited or occurs for unknown reasons. Recently, researchers discovered that pulmonary arterial smooth muscle cells within the walls of the pulmonary arteries of patients with IPAH show elevated levels of free calcium ion (Ca²⁺), indicating that high levels of Ca²⁺ may be critical stimuli for overgrowth of the smooth muscle cells. Ca²⁺ is controlled by several cellular mechanisms, one of which is the exchange of sodium and calcium on the cell membrane. The researchers will evaluate whether sodium/calcium exchange contributes to IPAH and if so, how. The information obtained from this research could be used to design drugs targeting specific molecules to treat IPAH.

MATTHEW EXLINE, MD

Ohio State University, Columbus, OH

Biomedical Research Grant • Co-Funded by the American Lung Association and the American Lung Association of the Midland States

Protein May Help Protect Against Death from Sepsis

Apoptosis In Sepsis: The Role Of Humanin, A Novel Anti-Apoptotic Peptide. Sepsis is a potentially deadly condition in which the body's immune system responds to a severe infection. However, it does not appear that patients with sepsis die from their infection directly. Recently, it has been suggested that septic patients die due to a weakening of the body's immune system through a process of cell suicide, called apoptosis. It has been shown in animal studies of sepsis that if apoptosis is halted then death from sepsis is reduced. Humanin is a protein that has been shown to block apoptosis. The researchers plan to verify that humanin is present in immune cells, and study whether humanin is reduced in the blood of septic patients. They will evaluate whether the concentration of humanin in the blood helps predict the outcome of a septic patient, and will investigate whether giving septic mice synthetic humanin will protect them against death, and if so, whether this is due to a reduction in apoptosis. This work will significantly improve the understanding of apoptosis in the immune system during sepsis and may lead to new therapies for septic patients.

FABEHA FAZAL, PhD

University of Rochester, Rochester, NY

Biomedical Research Grant • Funded by the American Lung Association

Blocking Excess Production Of A Protein May Lead To New Treatments For Lung Injury

Regulation Of Endothelial Intercellular Adhesion Molecule By Actin Dynamics. Thrombin is an enzyme that promotes blood clotting. It is released during sepsis and tissue injury. Upon its release, it interacts with blood vessel wall cells called endothelial cells and activates these cells. This activation process increases the production of a protein called ICAM-1 on the surface of endothelial cells, which promotes the binding of circulating white blood cells to the endothelium, the layer of cells that line the blood vessels. This binding promotes the migration of white blood cells across the endothelium to the site of inflammation, a process which is implicated in the development of acute lung injury. Although scientists have come to realize that ICAM-1 plays a crucial role in acute lung injury, the precise way

this protein is produced remains unclear. The researchers will study the regulation and the role of ICAM-1 in lung injury. This research may reveal ways to block excess production of ICAM-1, leading to new treatment targets for inflammatory diseases involving acute lung injury.

LAURA FREDENBURGH, MD

Brigham and Women's Hospital, Boston, MA

Biomedical Research Grant • Funded by the American Lung Association

COX-2 Enzyme May Play Key Role In Pulmonary Hypertension

Role Of Cyclooxygenase-2 In Hypoxia-Induced Pulmonary Hypertension And Vascular Remodeling.

Pulmonary hypertension is a disease of the blood vessels of the lung in which the pressure in the pulmonary arteries rises above normal levels and can become life-threatening. Pulmonary hypertension is incurable. Current treatment allows many patients with pulmonary hypertension to live for several years after their diagnosis. However, the disease usually leads to progressive right-sided heart failure as the blood vessels in the lung undergo changes known as vascular remodeling and the pressure in the pulmonary arteries continues to rise. New therapies that target the vascular remodeling process are desperately needed to halt progression of this incurable disease. Recently a class of medications called COX-2 inhibitors, which interfere with the COX-2 enzyme, has been found to increase the risk of heart attacks and stroke. The COX-2 enzyme may play a central role in the development of pulmonary vascular remodeling. The researchers hope to determine how the COX-2 enzyme affects the development of pulmonary hypertension and the progressive vascular remodeling that leads to worsening symptoms and death. This research eventually may lead to new therapies for this devastating disease process.

LAURA GONZALEZ BOSC, PhD

University of New Mexico, Albuquerque, NM

Dalsemer Research Grant • Funded by the American Lung Association

Uncovering How Pulmonary Arterial Hypertension Develops May Lead To New Therapy

Mechanisms Of NFATc3 Activation In A Model Of Chronic Hypoxia-Induced Pulmonary Hypertension.

Pulmonary arterial hypertension (PAH), abnormally high blood pressure in the arteries of the lungs, is a chronic and disabling condition. The underlying mecha-

nisms responsible for PAH are poorly understood. The complex process of developing PAH is driven, in part, by changes in gene expression (the process by which the information in a gene translates to proteins). The researchers will investigate the mechanisms that regulate changes in gene expression in PAH. A better understanding of these mechanisms will aid in the development of novel therapeutic approaches to prevent and cure this debilitating disease.

GABRIELE GRUNIG, PhD, DVM

St. Luke's-Roosevelt Hospital Center, New York, NY
Research Grant • Funded by the American Lung Association of the City of New York

Seeking Strategies To Stop Process That Leads To Pulmonary Hypertension

Inflammatory Model Of Pulmonary Arterial Remodeling And Hypertension. Pulmonary hypertension (PH) is a devastating, fatal disease that occurs in a large percentage of people with chronic obstructive pulmonary disease (COPD). PH is caused by the remodeling and constriction of blood vessels in the lungs, which leads to a decrease in the diameter of the vessels. This causes increases in the blood pressure in these vessels and corresponding increases in the pressure of the right heart. Some people have a genetic predisposition to PH, but other factors contribute to the development of the disease, including inflammation, lack of oxygen, and toxins. The researchers will use a mouse model to look for strategies to halt or reverse remodeling of lung blood vessels that lead to PH. They will investigate the genetic influence on the remodeling of pulmonary blood vessels. Their long-term goals are to identify processes that could be therapeutic targets for the inflammatory form of PH and to provide a mouse model that researchers can use to test large numbers of potential treatments.

JAMES HOTH, MD

Wake Forest University, Winston-Salem, NC
Biomedical Research Grant • Funded by the American Lung Association

Seeking Better Understanding Of Body's Response To Lung Injuries

Regulation Of Lung Injury By Toll-like Receptors After Pulmonary Contusion. A bruised lung, or pulmonary contusion, can result from blunt injuries such as those that might occur in an automobile accident. The effect of this injury can range from shortness of breath to death in up to 25% of afflicted patients. There

has been little meaningful improvement in treatment or outcome once a person sustains such a lung injury. This is due to a number of factors, including a lack of animal models where the biological responses to severe lung injury can be studied. The researchers will study a mouse model of pulmonary contusion, to examine the immune system's response to traumatic lung injury. This research will contribute to the understanding of lung trauma and enhance the ability to meet the current challenge of developing new and effective treatments for trauma patients.

PATTY J. LEE, MD

Yale University, New Haven, CT
Career Investigator Award • Funded by the American Lung Association

Investigating How The Lungs Defend Themselves Against Injury

Mechanisms Of VEGF And HO-1-Mediated Protection In Hyperoxic Lung Injury. Acute lung injury, known in its severe form as acute respiratory distress syndrome (ARDS), is a form of lung failure that occurs during infection or trauma. There is no specific therapy for this syndrome, which carries a 25 - 40% case fatality rate. Because it is not yet known how or why ARDS occurs, researchers are using high concentrations of oxygen, known as hyperoxia, which produce similar changes in the lungs, to mimic the damage that ARDS causes. Hyperoxia is commonly used as life-saving therapy in patients with profound loss of lung function, but prolonged use of hyperoxia can lead to inflammation, fluid accumulation, lung failure, and even death. The researchers are studying how two proteins, vascular endothelial growth factor (VEGF) and heme oxygenase-1 (HO-1) may help the lung defend itself against hyperoxia. The studies will allow them to identify potentially new and effective therapies against hyperoxic lung injury and ARDS.

ANA MORAN, MD

Baylor College of Medicine, Houston, TX
Research Training Fellowship • Funded by the American Lung Association of the Central States

Learning How To Prevent Lung Damage From Severe Traumatic Injury

Prevention Of Lung Apoptosis Following Shock/Trauma By Activation Of Stat3. Acute lung injury (ALI) occurs in up to 37% of patients suffering severe traumatic injuries and bleeding, and causes more than 70,000 deaths in the United States each year. Damage

and death of cells within the lung are key features of ALI; a better understanding of how lung cells are injured by severe traumatic injuries and bleeding is needed in order to develop effective treatments. The researchers will study how the important genes that keep lung cells alive are “turned on” following severe injury and bleeding and determine whether these genes can be stimulated by substances such as the protein interleukin-6. The long-term goals of this study are to gain an improved understanding of the mechanisms involved in lung damage during severe traumatic injury and bleeding, and to identify genes within the lung cells that are critical for lung damage prevention. Identification of these genes may lead to development of treatments, such as interleukin-6, that will result in prevention of ALI in patients following severe traumatic injuries and bleeding.

JEREMIE ROUX, PhD

University of California, San Francisco, San Francisco, CA
Senior Research Training Fellowship • Funded by the American Lung Association

Fluid Transport In The Lung Is Key To Treating, Preventing Acute Lung Injury

Role Of Stress Protein Response On IL-1Beta-Mediated Inhibition Of ENaC Expression And Function In Lung Epithelial Cells. Acute lung injury (ALI) is a devastating condition, with an overall death rate of 25 - 40%. Recent research has shown that in ALI, the body's normal process of removing excess fluid from the airspaces in the lung is reduced, impairing oxygenation of the blood. In previous studies, the researchers discovered that an inflammatory molecule named interleukin-1beta (IL-1beta), which is elevated in the lungs of patients with ALI, directly inhibits this fluid transport in the lung. A defense mechanism called the stress protein response (SPR) has been shown to interfere with IL-1beta and restore normal fluid transport across lung cells. However, the way in which this protection works is still unknown. The researchers will study the mechanisms of SPR and how they restore normal fluid transport across lung cells. The results of these experiments should set the stage for the development of potential new targets for treatment or prevention of acute lung injury.

SERGEI RYBALKIN, PhD

University of Washington, Seattle, WA
Biomedical Research Grant • Co-Funded by the American Lung Association and the American Lung Association of the Northwest

“Viagra” For The Lungs: Understanding How It Works May Improve Effectiveness

Characterization Of cGMP Phosphodiesterase (PDE5) Isoforms Expressed In Lung. Phosphodiesterase 5 (PDE5) is an enzyme (protein) produced in the lungs and other parts of the body that breaks down a substance called cyclic GMP. Cyclic GMP causes the blood vessels to widen. Sildenafil, well known as the drug Viagra, inhibits PDE5, leading to accumulation of cyclic GMP and widening of the blood vessels. Recently the U.S. Food and Drug Administration approved sildenafil under the brand name Revatio to treat pulmonary arterial hypertension (PAH), a life-threatening disease. The researchers will study the mechanisms of sildenafil's action on the lung. The research could lead to improved effectiveness and new applications for PDE5 inhibitors in the treatment of lung disorders.

YUNCHAO SU, MD, PhD

University of Florida, Gainesville, FL
Career Investigator Award • Funded by the American Lung Association of Florida

Investigating Protein That Can Lead To Blood Vessel Lesions In The Lungs

Cytoskeletal Regulation Of Endothelial Nitric Oxide Synthase In Lung Endothelial Cell Growth. Endothelial cells make up the inner layer of the lung's blood vessels. Cell growth and maintenance of lung endothelial cells require optimal nitric oxide production. Nitric oxide is synthesized by an enzyme called nitric oxide synthase. Disordered regulation of endothelial cell growth and nitric oxide synthase play important roles in blood vessel lesions in the lungs of patients with pulmonary hypertension and chronic obstructive pulmonary disease. During the growth of lung endothelial cells, there is an alteration in nitric oxide synthase activity which is caused by the cytoskeleton protein. The researchers will define ways of modifying the cytoskeleton protein and consequently controlling nitric oxide production and endothelial cell growth. Proving the role of cytoskeleton in the regulation of nitric oxide synthase during lung endothelial cell growth will help clarify the mechanism for the formation of blood vessel lesions and damage to the airways, and for tissue repair in the lungs of patients with chronic obstructive pulmonary disease.

COPD, SMOKING, AND AIR POLLUTION

Smoking is the major cause of chronic obstructive pulmonary disease (COPD), while air pollution can both cause and make the condition worse. The work of the American Lung Association has been critical in achieving a significant decline in cigarette smoking in the past 30 years, from 37.4 percent in 1970 to 20.8 percent in 2006, and in accomplishing important reductions in air pollution during the same time frame. Nevertheless, over 45 million adults still smoke; until recently, teenage smoking has been on the rise; and the American Lung Association estimates that some 136 million Americans live in counties with unhealthy levels of either ozone or particle pollution.

The American Lung Association supports a broad-based program of research into many aspects of COPD. Laboratory studies and patient-oriented investigations continue to look for answers to the fundamental questions of how the lungs and airways are damaged in COPD and what can be done to treat and prevent this destruction. Patient-centered studies are addressing such problems as the best way to assess and ensure quality of care. Other investigations are exploring genetic susceptibility to lung damage by cigarette smoke at the molecular level. In order to address the inordinately high level of smoking among American Indians and Native Alaskans, one group is testing the efficacy of an Internet site for smoking cessation which is designed to be culturally appropriate.

American Lung Association Scholar: COPD, Smoking, and Air Pollution



SAIRAM PARTHASARATHY, MD
Southern Arizona VA Health Care System
and the University of Arizona

Patients with chronic obstructive pulmonary disease (COPD), who are on mechanical ventilation in the ICU, usually remain on the breathing machine for longer than other patients. Although methods are available to predict the day-to-day chances of a patient being liberated from the ventilator, there is currently no way for doctors to predict how long a patient with COPD might stay on a ventilator, says Sairam Parthasarathy, MD, Assistant Professor of Medicine at the University of Arizona.

With a Biomedical Research Grant from the American Lung Association, Dr. Parthasarathy is investigating whether using a handheld ultrasound device can help doctors make such a prediction. Through his project, “Ultrasound Measure of Lung Hyperinflation in Chronic Obstructive Pulmonary Disease and Ventilator Dependence,” Dr. Parthasarathy hopes to show that this laptop-size device will allow doctors to better counsel patients and their families about how long they will be on ventilation and save costs by determining which patients can be transferred to a long-term acute care facility from the hospital if they will be on a ventilator for a prolonged period.

The handheld ultrasound device can help a doctor look at the position of the diaphragm, the main breathing muscle, to predict how much air is trapped in the lungs, an indication of how severe a patient’s COPD is. The ultrasound can also measure the thickness of the diaphragm, another predictive measure. Initial studies show the ultrasound device is both reliable and accurate in measuring the amount of air trapped in the lungs. Next, Dr. Parthasarathy will study how useful these measurements are in predicting whether a COPD patient will come off the ventilator.

“The American Lung Association grant has been instrumental in all of this research,” he says. “We hope to take this research to the next level using the information we have gained from this project.”

To see a complete description of Dr. Parthasarathy’s research project, please go to page 27.

JUN ARAYA, MD, PhD

University of California, San Francisco, San Francisco, CA
Junior Research Training Fellowship • Funded by the American Lung Association of California

Investigating Airway Wall Thickening In COPD

Integrin-Mediated Activation Of TGF-Beta In Airway Remodeling. One of the key features that predicts the severity of chronic obstructive pulmonary disease (COPD) is airway remodeling, changes that occur in the airway wall due to inflammation. One of the most important features of airway remodeling is the increase in the thickness of the airway wall due to proliferation of connective tissue cells called fibroblasts, and production of proteins such as collagen. Transforming growth factor (TGF-beta) is a potent molecule that helps regulate cell proliferation and collagen production. Recent research has suggested that molecules called integrins that are found on the surface of certain airway cells may help regulate TGF-beta in the airways. The researchers will study a particular integrin to determine whether it impairs airway wound healing and leads to wall thickening in COPD. This research may lead to novel therapeutic targets for COPD.

DAVID AU, MD

University of Washington, Seattle, WA
Career Investigator Award • Co-Funded by the American Lung Association and the American Lung Association of the Northwest

Importance Of Getting COPD Patients To Adhere To Therapy

Effect Of Medication Adherence On Outcomes And Costs Among Patients With Chronic Obstructive Pulmonary Disease. Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States. Drug therapy has become the mainstay of treatment for COPD, but there is little evidence about the effects of adhering to pharmaceutical therapy on the risk of death or COPD flare-ups. There is also no data about the effects of adhering to drug therapies on utilization of resources or cost of care. The researchers, by studying veterans receiving care in the Pacific Northwest, will address this gap by examining the effects of adhering to drug therapy on important patient-related outcomes including COPD flare-ups, death, and costs to the health care payer. The researchers hope to inform payers of medical care, health care systems, individual providers, and patients about the importance of adhering to medical therapy and identify those patients who may benefit from interventions that improve adherence to medical therapies.

CHRISTINE DALEY, PhD

University of Kansas, Kansas City, KS
Social Behavioral Research Grant • Funded by the American Lung Association

Internet Site On Smoking And Lung Health For American Indians And Alaska Natives

Educating American Indians And Alaska Natives About Smoking And Lung Health Using The Internet. Approximately 32% of American Indians and Alaska Natives (AI/AN) smoke cigarettes, compared with 22% of whites and 21.5% of African Americans, and have proportionately more lung health problems. In addition, tobacco has spiritual and cultural significance to many, though not all, AI/AN people. It is therefore necessary to provide AI/AN people with culturally appropriate education about tobacco and its health consequences. Currently, little such information is available and there are no Internet sites for these communities dedicated to tobacco and lung health. The researchers will develop such a site in three steps. Through focus groups, they will ask AI/AN community members about their Internet use for health information and types of information they would like to see about tobacco and lung health. They will develop the site and assess it for scientific accuracy, readability, cultural appropriateness, and ease of navigation. They will then conduct a second series of focus groups to show AI/AN community members the site, and to ask for recommended changes. When changes are incorporated, the researchers will then go live with the site.

STIJN DE LANGHE, PhD

Children's Hospital Los Angeles, Los Angeles, CA
Senior Research Training Fellowship • Funded by the American Lung Association

Insights Into Smooth Muscle Cells Can Help Premies And COPD Patients

Role Of Mesenchymal FGF Signaling In Lung Development. Smooth muscle cells are found around the airways. Defects in the development of smooth muscle cells lead to emphysema in adults and underdeveloped lungs in premature babies. The researchers will study smooth muscle cell precursors in the lung during embryonic development. These precursor cells respond to a family of growth factors. Preliminary research shows that this family of growth factors is critical to controlling the process by which smooth muscle cell precursors become smooth muscle cells. This study will help the researchers understand the role of this family of growth factors in the formation and maintenance of the smooth muscle cells

in normal and abnormal situations. The research will suggest novel strategies to encourage lung development in diseases of prematurity such as bronchopulmonary dysplasia, as well as treatment approaches for emphysema in older patients.

CHRISTOPHER EVANS, PhD

University of Texas MD Anderson Cancer Center, Houston, TX
Biomedical Research Grant • Co-funded by the American Lung Association and the Asociación Puertorriqueña del Pulmón with support from the American Lung Association of New England

Understanding Role Of Mucus Secretion In The Lungs

Role Of Muc5ac In Airway Homeostasis And Pathophysiology. Under healthy conditions, the airway surface is lined with a thin protective layer of secreted mucus. For people without chronic lung disease, suffering through an upper or lower respiratory tract infection that results in excessive mucus secretion is a nuisance. However, for people with asthma, chronic obstructive pulmonary disease, and cystic fibrosis, this so-called mucus hypersecretion is much more than just an annoyance. It appears, in fact, to play a pivotal role in determining the risk of death during an exacerbation of any of these diseases. Much is unknown about the positive and negative roles of mucus in these diseases. The researchers will test the influence of mucus secretion on airway obstruction by examining what happens when its key components are added in or taken away from the lung. They hope to identify potentially useful therapeutic targets that will help people with chronic lung disease.

SUSANNA HARJU, PhD

University of Washington, Seattle, WA
Senior Research Training Fellowship • Funded by the American Lung Association of the Northwest

Understanding How the Lung Protects Itself Against Noxious Agents

Role Of Matrilysin-Mediated E-Cadherin Shedding In Wound Healing. The epithelium is a layer of cells that protects the lungs against toxins, pollutants, and infectious agents, and initiates the body's inflammatory responses if the lungs are injured. Epithelial cells are tightly joined and establish a nearly impassable barrier to bacteria. Upon injury, these cells begin a series of responses to heal wounded tissue. It is likely that the lung's epithelial cells are constantly being subjected to minor injuries. The ability of these tissues to rapidly and efficiently repair these wounds is essential to restoring

the barrier function of the epithelium, and preventing the establishment of infection. The epithelium is chronically disrupted in a variety of lung conditions, such as COPD, cystic fibrosis, asthma, and cancer. The researchers will study two proteins, matrilysin (MMP-7) and E-cadherin, which are involved in wound repair in the lungs. Their study will contribute to a better understanding of the fundamental repair mechanisms of lung epithelium.

SUSAN LYNCH, PhD

University of California, San Francisco, San Francisco, CA
Research Grant • Funded by the American Lung Association of California

Unlocking The Role Of Bacteria In COPD Flare-Ups And Remissions

Analysis Of Bacterial Community Dynamics In Adult Patients With Exacerbations Of Chronic Obstructive Pulmonary Disease. Although bacteria are now thought to be responsible for up to 50% of COPD episodes, little is known about the types and dynamics of bacteria in the airways of people with the disease. Recently, it has been shown that bacterial communities exist in a number of respiratory diseases. To fully understand the contribution of specific members of the airway bacterial community to COPD, it is necessary to identify which bacteria are present when patients develop symptoms. The researchers use a novel tool that allows them to comprehensively describe the types of bacteria present in the airways of COPD patients during flare-ups and remission. They will look at how the microbial community changes over time and with antimicrobial treatment and which microbes are associated with disease progression. Eventually, this research may lead to new treatments for COPD.

ANJAPARAVANDA P. NAREN, PhD

University of Tennessee, Memphis, TN
Career Investigator Award • Funded by the American Lung Association

How Does The Lung Protect Against Tobacco Carcinogens?

Cooperative Regulation Of MRP2 And CFTR In Lung Epithelial Cells. These researchers are studying how the lungs attempt to fight against tobacco-specific carcinogens from tobacco smoke. The researchers are looking at whether the epithelial cells that line the airways of the lung activate two transporters—multidrug resistance protein-2 (MRP2) and cystic fibrosis transmembrane conductance regulator (CFTR)—in response to cigarette smoke entering the airways. MRP2 may

pump out the carcinogens, while CFTR pumps out salt and watery mucus which help wash out the carcinogens into the sputum. The researchers hope to gain a better understanding of how these two substances work cooperatively to contribute to the health of the lung and to act as a first line of defense against cigarette smoking. The researchers also will investigate whether CFTR and MRP2 functionality is impaired in patients suffering from smoke-related diseases compared with healthy individuals.

SAIRAM PARTHASARATHY, MD

Southern Arizona VA Health Care System and the University of Arizona, Tucson, AZ
Biomedical Research Grant • Co-funded by the American Lung Association and the American Lung Association of the Southwest

Why Are Some Patients With COPD Dependent On A Mechanical Ventilator?

Ultrasound Measure Of Lung Hyperinflation In Chronic Obstructive Pulmonary Disease And Ventilator Dependence. Patients with chronic obstructive pulmonary disease (COPD) are unable to breathe comfortably because they have excess air trapped inside their lungs. Some patients with COPD are unable to breathe on their own, and therefore remain dependent on the mechanical ventilator, or “life support.” Currently, it is not known exactly why such patients are unable to breathe on their own, but it is thought that excess air trapped in the lungs may be one of many reasons. The researchers will test a novel method that uses ultrasound techniques to detect air trapped in patients’ lungs while they are breathing with the help of a life support machine. They hope to find whether such air trapping plays an important role in a patient’s dependence on the life support machine. They hope that in the future, such a test can help them select the ideal candidates for new methods that help reduce air trapping and thereby liberate patients from life support.

JOSEPH M. PILEWSKI, MD

University of Pittsburgh, Pittsburgh, PA
Career Investigator Award • Funded by the American Lung Association of the Mid-Atlantic

A Safe And Simple Way To Clear Mucus From The Airways

Effect of Bicarbonate on Mucociliary Clearance. Airway obstruction by mucus contributes significantly to the development of progressive respiratory disease in people with chronic bronchitis and bronchiectasis,

chronic inflammatory airway diseases. Mucus obstruction also plays a role in asthma episodes. This project is examining whether inhaled bicarbonate can increase the clearance of mucus in a laboratory model of lung cells, and in patients with these conditions; subsequent studies will assess whether pulmonary function improves when mucus clearance is increased. Although inhaled bicarbonate is not expected to cure chronic bronchitis, bronchiectasis, or asthma, it may offer an inexpensive, safe means of treatment that is widely applicable and easy to administer, and it may prove to delay the progression of lung disease by improving airway clearance.

YUN M. SHIM, MD

University of Virginia, Charlottesville, VA
Research Grant • Funded by the American Lung Association of the Atlantic Coast

Why Do Only Some Smokers Develop COPD?

Leukotriene Biosynthetic Pathways In The Pathogenesis Of Emphysema. Fewer than 25% of smokers end up developing significant chronic obstructive pulmonary disease (COPD), and more than 15% of COPD-related deaths occur in non-smokers. This suggests significant contribution of individual genetic background and other inciting factors in the development of COPD. The researchers will study two types of molecules involved in inflammation, interleukin-13 (IL-13) and leukotrienes, to see whether they play a role in determining who develops COPD from cigarette smoke exposure. The researchers will recruit 30 patients in each of four categories: patients with emphysema, patients with chronic bronchitis, cigarette smokers without lung problems, and people who have never smoked cigarettes. They will measure IL-13 and leukotrienes in each group. Their research could provide valuable information about who is at high risk of developing COPD from cigarettes. The researchers hope this initial study will grow into a large study to find and characterize a person’s predisposition to developing different types of COPD.

MARTIN STEFFEN, MD, PhD

Boston University, Boston, MA

Biomedical Research Grant • Funded in partnership between the American Lung Association of New England and the Alpha-1 Foundation

Key Protein In Development Of COPD Could Shed Light On Genetics Of The Disease

An Exploration Of Proteasome Structure And Function In COPD. Chronic obstructive pulmonary disease (COPD) is a complex respiratory disease characterized by decreased airflow and abnormal inflammation. The researchers will explore one potential cause of the abnormal inflammatory response, and how that inflammation may promote disease development. They will focus on the proteasome, a key protein complex known to regulate several processes which cause inflammation, and which has previously been implicated in the development of diabetes and heart disease. They will isolate proteasome complexes from people with and without COPD, in order to identify differences between the two groups. Specifically, they will compare the protein and chemical composition of the complexes, and test their functional activity. A positive finding of consistent differences, along with their previous data, will help establish the proteasome as a source of genetic risk for the disease, which can then be used to develop a test to identify susceptible individuals. They also will be prepared to explore the use of drugs that modulate proteasome activity to treat people with this deadly disease.

TUBERCULOSIS

Tuberculosis (TB) remains an important disease in the United States and a worldwide epidemic that kills approximately 1.6 million people each year. Since it is transmittable and more and more people are migrating or traveling around the world, this international problem is of great concern to Americans. The worldwide AIDS epidemic has reached frightening proportions and is partly responsible for the increase in TB internationally, as the two infections often coexist. More recently, Americans have learned about the potential threat of a deadly form of TB germ which has no effective therapy and kills rapidly.

The basic cellular and immune processes that initiate and control TB infection are being studied, as are the molecules and genes in the TB germ that enable it to infect humans and become resistant to drugs. A greater understanding of how the body's immune system protects against TB and why this defense system sometimes fails is being sought. Studies such as these will provide a solid foundation for developing a better vaccine. Other studies focus on why HIV infection increases susceptibility to TB infection.

American Lung Association Scholar: Tuberculosis



RUSSELL KARLS, PhD
University of Georgia

Russell Karls, PhD, is testing a novel idea for a new tuberculosis (TB) vaccine. To obtain government funding for his research, he must first demonstrate that his hypotheses are correct, and he hopes to do just that with funding from his Biomedical Research Grant from the American Lung Association. Through his project, “Testing a Novel Tuberculosis Mucosal Vaccine,” Dr. Karls is studying the role of lung epithelial cells in the disease process of TB.

Lung epithelial cells normally provide a barrier against respiratory infection. The lungs also contain a limited number of immune cells called phagocytes that patrol the lungs and engulf microbes before they can breach the epithelial cell barrier.

Early in the infection process, TB bacteria that successfully invade epithelial cells replicate efficiently inside and avoid detection and destruction by phagocytes. The increased numbers of bacteria released from the infected cells present a challenge for the phagocytes to quickly catch and engulf all of the bacteria before some invade other cells in the body. “The longer bacteria can replicate undetected by the immune system, the greater their survival advantage,” says Dr. Karls, a research scientist at the University of Georgia. He will study mutant TB bacteria that lack a gene that may aid in the invasion of, replication in, or spread between lung epithelial cells and compare them with normal TB bacteria. “We hope to see much reduced survival and dissemination from the lungs by the mutant strain because it is unable to replicate undetected inside of lung epithelial cells and is more likely to be gobbled up by phagocytes,” Dr. Karls says. “We hope this mutant will form the basis of a new TB vaccine.”

To see a complete description of Dr. Karl’s research project, please go to page 31.

CHRISTOPH GRUNDNER, PhD

University of California, Berkeley, Berkeley, CA
Research Training Fellowship • Funded by the American Lung Association of California

How Do Two Proteins Help TB Bacterium Escape The Immune System's Defenses?

Structure And Function Of The Mycobacterium Tuberculosis Virulence Factors PtpA And PtpB.

Tuberculosis claims 1.6 million lives a year. Many TB patients show resistance to treatment with currently available drugs, and no new drugs have been introduced since the early 1960s. The cause of TB, called *Mycobacterium tuberculosis* (Mtb), infects macrophages, cells of the immune system that usually eliminate bacterial infections. Mtb survives in macrophages by turning off a number of mechanisms by which the macrophage kills bacteria. To do so, Mtb and other bacteria make specialized proteins called virulence factors. Two likely candidates that contribute to the escape of Mtb from the macrophage immune defenses are called PtpA and PtpB. The researchers will study these two proteins, in order to gain valuable insights into how to counter their effects. A drug that targets the Ptps may help the immune system to more rapidly cure TB.

RUSSELL KARLS, PhD

University of Georgia Research Foundation, Athens, GA
Biomedical Research Grant • Funded by the American Lung Association

Building A Better Tuberculosis Vaccine

Testing A Novel Tuberculosis Mucosal Vaccine. A vaccine for tuberculosis, BCG, has been used for decades, but a more effective vaccine is needed. The researchers will study how the *Mycobacterium tuberculosis* bacteria escape early destruction by the immune cells. These bacteria establish infection when inhaled into the alveoli (air sacs of the lungs). Interactions of the tuberculosis bacteria with cells within the alveoli are critical to the infection process and may impact whether the infection is contained at the initial contact site or spreads to other parts of the body. The researchers will study the function of a *M. tuberculosis* gene that appears to affect the fate of cells that line the walls of the alveoli. They will study if tuberculosis bacteria lacking this gene can no longer replicate in, or spread from, the alveolar lining. Bacteria that cannot infect the cell lining are more likely to be engulfed by immune cells that patrol the alveoli. The information gathered from this research will aid in the development of an effective tuberculosis vaccine.

MARK LANG, PhD

Dartmouth Medical School, Lebanon, NH
Biomedical Research Grant • Funded by the American Lung Association with support from the American Lung Association of New England

New Clues To Immune System's Response To TB Bacteria Could Lead To New Vaccine

Novel Cellular Interactions And Humoral Immunity To M. Tuberculosis. One-third of the world's population is infected with *Mycobacterium tuberculosis*, the bacteria that causes tuberculosis. There are 8.8 million new cases of tuberculosis and 1.6 million TB deaths each year. The increasing incidence of infection with multi-drug-resistant tuberculosis strains in wealthier nations such as the United States is alarming. One of the most tragic aspects of tuberculosis is that millions of lives could be saved every year by the development of novel vaccines to complement the existing Bacillus Calmette-Guerin (BCG) vaccine. The BCG vaccine confers limited protection and a booster vaccine is desperately needed to ensure adequate protection. Despite impressive advances in the field, development of such a vaccine has been difficult, in part because researchers have insufficient knowledge of the immune system's response to *M. tuberculosis* and how to best stimulate protective immunity. The researchers will study newly discovered aspects of the immune response to *M. tuberculosis* that lead to long-term immunity, and may guide future vaccine strategies. They will focus on the body's humoral immune responses, or the immune system's production of antibodies.

NAIMISH PATEL, MD

Beth Israel Deaconess Medical Center, Boston, MA
Biomedical Research Grant • Funded by the American Lung Association of New England and the Massachusetts Thoracic Society

Unlocking How HIV Increases Susceptibility To TB

HIV Alters Macrophage Apoptotic Response To M. Tuberculosis Through IL-10. While the HIV epidemic has resulted in an increased rate of tuberculosis worldwide, the manner in which HIV increases susceptibility to TB disease is poorly understood. TB is caused by a bacterium called *Mycobacterium tuberculosis*, which is transmitted when a person breathes in the TB bacterium. Specialized lung immune cells called alveolar macrophages serve as the first line of defense against TB bacteria. The bacteria are believed to cause disease by successfully existing inside alveolar macrophages without being killed or detected. Macrophages undergo

programmed cell death, a normal suicidal process to selectively remove cells that are no longer needed, damaged or are dangerous. Programmed cell death prevents TB bacteria from existing undetected in infected cells. The investigators' preliminary research suggests that HIV infection of macrophages hinders the normal cell death response of macrophages, making a person more susceptible to TB infection. The researchers seek to further study the mechanism by which HIV is able to prevent cell death and also to identify factors in the lung's immune defense that are responsible for this effect. They will also identify potential novel targets for TB therapy in HIV, which can provide critical information for applications such as vaccine development.

ROXANA ROJAS, MD, PhD

Case Western Reserve University, Cleveland, OH
Biomedical Research Grant • Co-Funded by the American Lung Association and the American Lung Association of the Midland States

Gaining Insight Into How TB Germ Hides From Immune System

Regulation Of CD4+ T Cell Adhesion And Migration Induced By Mycobacterial Phosphatidylinositol Mannosides. Tuberculosis (TB) is a bacterial disease that primarily affects the lungs and is caused by *Mycobacterium tuberculosis*. Many studies have shown that control of infection requires an intact, healthy immune system. However, control of infection does not eliminate all organisms from the lung and this state is called latent TB. Persons infected with *M. tuberculosis* are at risk of having the latent bacteria become reactivated, especially people with suppressed immune systems such as those with HIV infection. There is a need to improve therapy against TB as well as develop preventive measures such as vaccines. Knowing how *M. tuberculosis* escapes recognition by the immune system and remains latent is important to design new approaches for TB control. *M. tuberculosis*' immune evasion mechanisms can affect two types of cells: macrophages and T-lymphocytes. The researchers will study how *M. tuberculosis* affects T-lymphocytes and regulates their functions. Ultimately this research will contribute to efforts to develop more effective therapies and vaccines against TB.

JOANNE TURNER, PhD

Ohio State University, Columbus, OH
Career Investigator Award • Co-funded by the American Lung Association and the American Lung Association of the Midland States

Predicting When Tuberculosis Will Become Infectious

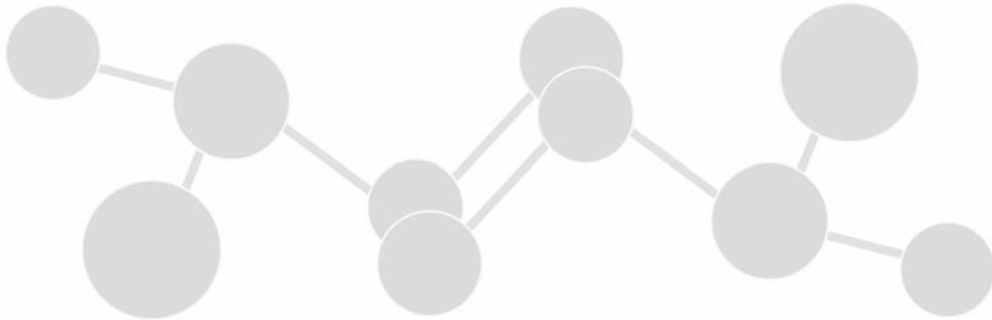
In Vitro Predictors Of Susceptibility For Reactivation Tuberculosis. Approximately one-third of the world's population is infected with *Mycobacterium tuberculosis*, the germ that causes tuberculosis. However, only a small portion of those individuals will actually develop active infectious disease. This discrepancy is due to the ability of *M. tuberculosis* to persist within the body for many years in a form often referred to as latency. In some people, this persistent infection is followed by a period of active bacterial growth that produces symptoms of disease and the ability to transmit *M. tuberculosis* to others. This form of infection is called reactivation. The researchers are using a mouse model to try to identify immunological markers that change prior to reactivation, which could then be used to predict when reactivation would occur. This would provide an extremely powerful tool for the identification of individuals who are progressing to reactivation disease and ultimately result in timely intervention and reduced disease transmission. Detection and treatment of individuals before they become infectious to others could have a substantial impact on the incidence of global tuberculosis.

OTHER LUNG INFECTIONS

Lung infections are common and often deadly. Influenza (flu) and pneumonia-related illnesses are responsible for approximately 62,000 deaths annually. Studies are being done to understand human susceptibility to the most dangerous flu viruses. American Lung Association researchers continue to study a bacterium called pseudomonas, which affects the injured lungs of people who have chronic obstructive pulmonary disease (COPD) and cystic fibrosis, hoping to find a new means of prevention.

American Lung Association researchers are studying a wide variety of other lung infections in the quest for better ways to prevent and heal them. Among those being investigated are HIV infections, RSV, which is a major problem in children, and fungal infections. How bacterial infections complicate the flu and COPD is receiving renewed attention.

American Lung Association Scholar: Other Lung Infections



SANTANU BOSE, PhD

University of Texas Health Science Center at San Antonio

While human respiratory syncytial virus (RSV) is usually thought of as a disease of infants, this airborne virus that infects lung cells can also affect the elderly. “A study published several years ago found that 14,000 elderly Americans die of RSV-related pneumonia every year,” says Santanu Bose, PhD. “Just as young children are at risk of RSV in daycare centers, the elderly risk catching RSV in nursing homes.”

With an American Lung Association grant, Dr. Bose is studying an enzyme whose production in cells results in lowering of cholesterol as a potential antiviral agent against RSV. Since many viruses, including RSV, require cholesterol for infection, the researchers will study whether this enzyme, called cholesterol 25-hydroxylase (C25H), acts as an anti-RSV agent.

“We are planning to study elderly admitted to a VA hospital to find co-relation of statin usage (medication used to lower high cholesterol) and pneumonia caused by RSV,” Dr. Bose says. “We have preliminary results to believe that patients who had been taking statins had a low level of RSV and other respiratory pathogens. Cholesterol is important for RSV infection. If there is less cholesterol in the cells, then RSV can’t infect the cells.”

In addition to his work on cholesterol and RSV, Dr. Bose has been able to expand his research on RSV thanks to the Lung Association grant. He is also studying proteins called defensins, which are another component of lung cells’ antiviral response.

Dr. Bose’s long-term goal is to produce results that could be used to develop antiviral therapies against RSV and other respiratory viruses that cause pneumonia. Currently there is no effective antiviral therapy or vaccine to combat RSV.

To see a complete description of Dr. Bose’s research project, please go to page 35.

SANTANU BOSE, PhD

University of Texas Health Science Center, San Antonio, TX
Biomedical Research Grant • Funded by the American Lung Association

Can Enzyme That Lowers Cholesterol In Cells Lead To Treatment For RSV?

Role Of Cholesterol 25-Hydroxylase During NF- κ B Dependent Innate Anti-Viral Response Against Human Respiratory Syncytial Virus. Human respiratory syncytial virus (RSV) is an airborne virus that infects lung cells to cause a wide variety of diseases among infants, children, and the elderly. RSV infection is associated with high death rates among children, but there is currently no effective anti-viral therapy or vaccine to combat RSV infection. In an effort to identify novel anti-viral factors against RSV, the researchers will study the anti-viral defense mechanisms of lung cells. They have identified a candidate anti-viral protein called cholesterol 25-hydroxylase (C25H). This is an enzyme whose production in cells results in lowering of cellular cholesterol content. Since many viruses, including RSV, require cholesterol for infection, the researchers will study whether C25H acts as an anti-RSV agent, and will study the way in which it restricts RSV infection. These studies may lead to the development of novel anti-viral therapies against RSV and other respiratory viruses.

JOHN BOUCHER, PhD

University of Texas at Tyler, Tyler, TX
Biomedical Research Grant • Funded by the American Lung Association of the Central States

Targeting Protein On Bacteria That Causes Lung Infections

The Role Of IcmP, A *Pseudomonas Aeruginosa* Insulin-Cleaving Metalloprotease. *Pseudomonas aeruginosa* is a type of bacteria associated with many types of infections including those of the lungs. *Pseudomonas* infections of the lung are typically seen in patients who suffer from cystic fibrosis, HIV, and cancer. The ability of organisms such as *P. aeruginosa* to cause disease is dependent on proteins and other factors that they produce. Many of these proteins are found within the cells themselves. However, some are located on the outside of the cell anchored into the membrane. *P. aeruginosa* has a membrane with two layers, with the outer one functioning as a protective barrier. Some proteins on the outer membrane are responsible for adhering to or entering the body, thereby causing disease. These outer membrane proteins may also evade the body's immune system. The researchers are studying one of the *P. aeruginosa* outer membrane proteins called IcmP. Investigation into the

function of this protein may lead to identification of new drug targets and vaccines, both of which would prevent *P. aeruginosa* from causing disease.

THOMAS FREDERICK BYRD III, MD

University of New Mexico, Albuquerque, NM
DeSouza Research Award • Funded by the American Lung Association of the Southwest

Preventing A Bacterial Infection From Becoming Invasive

The Role Of *Mycobacterium Abscessus* Glycopeptidolipid In Colonization And Invasion.

Mycobacterium abscessus, a type of germ known as non-tuberculous mycobacteria, can colonize in the airways of the lung. Although in most cases this colonization does not cause severe illness, it does pose a danger for some people, including patients with cystic fibrosis. During the course of colonization, these bacteria can become invasive and enter the lung from the airways, resulting in pneumonia and life-threatening illness. The bacterial factors that are involved in the switch from colonization to invasion are not understood. The researchers have identified a molecule on the surface of *M. abscessus* that is involved in the switch from colonization to invasion. They will study how this molecule is involved in colonization and how it is regulated. These studies have the potential to lead to new therapeutic interventions to prevent lung colonization by *M. abscessus* and other non-tuberculous mycobacteria, thereby preventing subsequent invasive disease.

CORNELIUS CLANCY, MD

University of Florida, Gainesville, FL
Career Investigator • Funded by the American Lung Association of Florida

Seeking Proteins Essential To Mold-Related Lung Infection

Identification Of Virulence Factors During Invasive Pulmonary Aspergillosis (IPA). Invasive pulmonary aspergillosis (IPA) is an infection of the lungs caused by mold called *Aspergillus fumigatus*. Humans normally inhale several hundred *A. fumigatus* spores into their lungs every day. If they do not have a deficient immune system, people might develop allergic symptoms upon inhaling the spores but do not develop more extensive disease. If a person's immune system is damaged, however, the spores might not be cleared from the lungs, in which case they can proliferate and invade into surrounding tissue and blood vessels. The resulting disease, IPA, has become markedly more common as the numbers of people with compromised immune systems have in-

creased due to medical advances. Even with aggressive therapy with antifungal drugs, over half of patients with IPA die from the disease. The researchers will study the mechanisms by which *A. fumigatus* cause IPA. They have used antibodies made by patients who survived IPA to identify 25 *A. fumigatus* proteins that are expressed by the mold within the lungs. They will study five of these proteins to see whether they are essential to the disease process and represent potential targets for drugs or vaccines.

PATRICIA DUBIN, MD

Children's Hospital of Pittsburgh, Pittsburgh, PA
Biomedical Research Grant • Support of this grant comes from the Mary Fuller Russell Research Fund

Seeking Key To Immune System's Response To Deadly Pneumonia Bacteria

IL-23 And Pseudomonas Aeruginosa Pneumonia. The bacterium *Pseudomonas aeruginosa* causes pneumonia in individuals who are on a ventilator, as well as people whose immune systems are compromised due to cystic fibrosis, AIDS, low birth weight, or other causes. Some studies show that when *P. aeruginosa* infection spreads from the initial site of infection, through the bloodstream, more than 50% of the infected individuals will die. In spite of many advances in medical care, this figure has not improved in the last 20 years. Though *P. aeruginosa* is often blamed for the significant lung damage associated with infection, the immune system is also responsible. The researchers will study IL-23, a molecule produced by the immune cells that first recognize *P. aeruginosa* in the lung. Understanding the mechanism of IL-23 will provide significant insight into the immune system's response to *P. aeruginosa*. This knowledge will lay the groundwork for ultimately developing the treatments against *P. aeruginosa* infection, allowing doctors to prevent, rather than respond to, lung damage and subsequent illness.

DANNY HSIA, MD

University of Washington, Seattle, WA
Junior Research Training Fellowship • Funded by the American Lung Association of the Northwest

Predicting Which Children With RSV Will Develop Asthma

Exhaled Nitric Oxide Output In Infants With Pulmonary Hyperinflation Following Respiratory Syncytial Virus Bronchiolitis. Most lower respiratory tract illnesses with wheezing that occur in the first three years of life are associated with infection with respira-

tory syncytial virus (RSV). Many studies have shown an association between RSV, subsequent wheezing, and the development of asthma. Between 20-40% of young children who have RSV suffer from recurrent wheezing episodes that resolve on their own as the child gets older. A major challenge for doctors is predicting which infants are at increased risk for developing asthma after RSV and which will resolve on their own. The researchers will use two measurements to see how each alone and in combination predicts recurrent wheezing as the child grows. One measurement, called the thoracic index, measures persistent airway narrowing, while the nitric oxide index measures ongoing airway inflammation. If these measurements prove useful, they will allow doctors to identify which children who have had RSV might benefit from asthma therapy very early in life and avoid complications of asthma in very young children.

SAMITHAMBY JEYASEELAN, DVM, PhD

National Jewish Medical and Research Center, Denver, CO
Biomedical Research Grant • Support of this grant comes from the Mary Fuller Russell Research Fund

Gaining Insight Into Immune System's Response To Bacteria During Pneumonia

Pulmonary Innate Defense Against Vacuolar Pathogens Using Legionella Pneumophila As A Model. Bacterial pneumonia affects more than one million adults in the United States and causes 30,000 deaths per year. Although some advances have been made in the recent past in understanding bacterial pneumonia, there are still no effective control measures. The majority of bacterial pneumonia is caused by germs that live and multiply in a structure inside cells called vacuoles. The researchers will explore the immune system's response to these vacuole-enclosed bacteria using *Legionella pneumophila* as a model. They will focus on recently discovered receptors called toll-like receptors, or TLRs, which sense the presence of germs and trigger a cascade of signals in immune cells. These signals lead to the body's immune system responses, which help eliminate the intruding germs. There is an immediate need for a safe and efficient vaccine to control pneumonia germs that cause devastating lung disease. Understanding how to manipulate the body's immune response to these germs could provide an important target for the development of an efficient vaccine against pneumonia without adverse side effects.

GEORGETTE KANMOGNE, PhD

University of Nebraska, Omaha, NE

Career Investigator Award • Funded by the American Lung Association

Identifying Cause Of Common Lung Complication In AIDS Patients

Mechanisms Of HIV-1 gp120-Induced Vascular Injury And AIDS Pulmonary Complications. The lung is a major target for HIV infection and complications of AIDS. AIDS patients usually die from complications of AIDS, including manifestations of acute lung injury such as pulmonary hypertension (abnormally high blood pressure in the arteries of the lungs). How HIV infection leads to pulmonary hypertension is not known; however, it is thought that special immune cells called endothelial cells located on the lung blood vessels are damaged or dysfunctional in patients with pulmonary hypertension. The researchers are studying an HIV surface protein called gp120, to see whether these proteins directly cause endothelial cell injury in the lung and lead to the development of HIV-related pulmonary hypertension. The results of this study will be important for developing novel therapeutic approaches to prevent lung diseases in HIV-infected patients.

MARGARETHE (META) J. KUEHN, PhD

Duke University, Durham, NC

Career Investigator Award • Funded by the American Lung Association

Seeking Ways To Block Bacteria From Delivering Toxins To Lung Cells

Production And Virulence Properties Of P. Aeruginosa Vesicles. The bacterium *Pseudomonas aeruginosa* causes a significant number of infections and deaths in both AIDS and cystic fibrosis patients. *P. aeruginosa* is highly resistant to antibiotics, so there is an urgent need for new ways to combat this deadly organism. The goal of this research is to understand a mechanism that may contribute to the virulence of *P. aeruginosa*. The researchers are studying the production of vesicles, which are small round portions of the cell that are abundantly secreted by *P. aeruginosa*. Toxic products within the vesicles are directed into lung cells, where they can inflict damage. The study aims to understand how this process works, so that therapeutics can be designed to block vesicle production and their ability to harm host cells, thereby protecting lung patients from the devastating effects of *P. aeruginosa* infections. Insights from this study could also pinpoint new antimicrobial targets in similar bacterial pathogens that infect the respiratory tract.

KEVIN LEGGE, PhD

University of Iowa, Iowa City, IA

Biomedical Research Grant • Co-Funded by the American Lung Association and the American Lung Association of the Upper Midwest

Finding A Way To Help The Immune System Fight Off Bacterial Infections After Influenza

Respiratory Dendritic Cells: Cell Migration And Induction Of Adaptive Immunity During Virus Infections. The lungs are routinely exposed to foreign pathogens such as bacteria and viruses in the air that we breathe. Often our immune system halts these pathogens before significant infections can occur. However when these pathogens do establish an infection, the immune system must kick in to fight it. In the lungs, respiratory dendritic cells (rDC) are thought to be responsible for inducing this immune system response. The researchers have found that following influenza infections, rDC rapidly migrate from the lungs to the lymph nodes and induce an immune response that is specific to influenza. But within 24 hours after influenza virus infection, rDC halt their migration. This halt is of particular concern following respiratory virus infections, where concurrent or new bacterial infections are common. The researchers will study the way in which rDC migration is stopped following influenza virus infections. They will then determine if manipulating this mechanism can restore rDC migration, thus helping the immune system fight off secondary infections. By boosting the immune system's response to bacterial infections, complications ranging from otitis media and pneumonia in children to potentially deadly pneumonia in elderly adults might be avoided.

SUSAN LYNCH, PhD

University of California, San Francisco, San Francisco, CA

Research Grant • Funded by the American Lung Association of California

Unlocking The Role Of Bacteria In COPD Flare-Ups And Remissions

Analysis Of Bacterial Community Dynamics In Adult Patients With Exacerbations Of Chronic Obstructive Pulmonary Disease. Although bacteria are now thought to be responsible for up to 50% of COPD episodes, little is known about the types and dynamics of bacteria in the airways of people with the disease. Recently, it has been shown that bacterial communities exist in a number of respiratory diseases. To fully understand the contribution of specific members of the airway bacterial community to COPD, it is necessary to identify which bacteria are present when patients develop symptoms.

The researchers use a novel tool that allows them to comprehensively describe the types of bacteria present in the airways of COPD patients during flare-ups and remission. They will look at how the microbial community changes over time and with antimicrobial treatment and which microbes are associated with disease progression. Eventually, this research may lead to new treatments for COPD.

BORNA MEHRAD, MD

University of Texas Southwestern Medical Center, Dallas, TX
Career Investigator Award • Funded by the American Lung Association

Searching For Genetic Clues To Resistance To Pneumonia

Genetically Determined Host Resistance To Pneumonia. Pneumonia caused by gram-negative bacteria is a common and serious illness, but relatively little is known about inherited factors that predispose a person to this infection. The researchers have identified a strain of mouse that is much more resistant to this infection than another more common strain. These two strains of mice are nearly identical, except for one set of genes. In this study, the researchers hope to determine how the resistant animals fight off the infection more effectively. These experiments should produce results relevant to human disease in two ways. First, it is possible that some humans have genes similar to those that make mice more resistant to pneumonia. Second, understanding the way in which the resistant mice fight off the infection could lead to new treatments to help patients fight off the infection in similar ways.

THOMAS A. MOORE, PhD

University of Michigan, Ann Arbor, MI
Career Investigator Award • Funded by the American Lung Association of the Midland States

Looking For Genes That Make Pneumonia Bacteria Especially Powerful

Molecular Identification Of *Klebsiella Pneumoniae* Virulence Genes Using A Murine Model Of Pneumonia. *Klebsiella pneumoniae* is the leading cause of a type of bacterial pneumonia known as gram-negative pneumonia, which results in severe infection with high death rates if it is not treated. There is great concern about the recent emergence of multidrug resistance seen in *K. pneumoniae*. The increasing limitations of conventional antibiotic treatment underscore the importance of understanding how *K. pneumoniae* infects the body. The researchers will investigate whether

highly infectious strains of *K. pneumoniae* contain unique genes that make the germ especially powerful and able to overcome the body's immune defenses. Results from this study will further the understanding of how *K. pneumoniae* works in the body and potentially identify targets for future treatments.

JESSICA MORELAND, MD

University of Iowa, Iowa City, IA
Career Investigator Award • Funded by the American Lung Association of the Upper Midwest

Examining The Body's Response To Common Cause Of Bacterial Pneumonia

Neutrophil-Endothelial Cell Interactions Elicited By *S. Pneumoniae* In The Lung. Bacterial pneumonia caused by *Streptococcus pneumoniae* is an extremely common illness. It is estimated that 1 million children die each year from pneumococcal pneumonia worldwide, and more than 500,000 cases of pneumonia each year are caused by *S. pneumoniae* in the United States alone. The researchers will study early events in the body's response to *S. pneumoniae* that initiate the movement of white blood cells from within the bloodstream to the lung, and may enhance the ability of the white blood cell to attack and kill the bacteria that is causing pneumonia. The researchers hope that gaining a better understanding of the way in which the body's immune system responds to *S. pneumoniae* will lead to better treatments for this most common cause of bacterial pneumonia.

NAIMISH PATEL, MD

Beth Israel Deaconess Medical Center, Boston, MA
Biomedical Research Grant • Funded by the American Lung Association of New England and the Massachusetts Thoracic Society

Unlocking How HIV Increases Susceptibility To TB

HIV Alters Macrophage Apoptotic Response To *M. Tuberculosis* Through *IL-10*. While the HIV epidemic has resulted in an increased rate of tuberculosis worldwide, the manner in which HIV increases susceptibility to TB disease is poorly understood. TB is caused by a bacterium called *Mycobacterium tuberculosis*, which is transmitted when a person breathes in the TB bacterium. Specialized lung immune cells called alveolar macrophages serve as the first line of defense against TB bacteria. The bacteria are believed to cause disease by successfully existing inside alveolar macrophages without being killed or detected. Macrophages undergo

programmed cell death, a normal suicidal process to selectively remove cells that are no longer needed, damaged or are dangerous. Programmed cell death prevents TB bacteria from existing undetected in infected cells. The investigators' preliminary research suggests that HIV infection of macrophages hinders the normal cell death response of macrophages, making a person more susceptible to TB infection. The researchers seek to further study the mechanism by which HIV is able to prevent cell death and also to identify factors in the lung's immune defense that are responsible for this effect. They will also identify potential novel targets for TB therapy in HIV, which can provide critical information for applications such as vaccine development.

LEE QUINTON, PhD

Harvard University School of Public Health, Boston, MA
Senior Research Training Fellowship • Co-funded by the American Lung Association and the American Lung Association of New England

Targeting The Immune System's Response To Bacterial Pneumonia

IL-6 Family Cytokines And Alveolar Epithelial STAT3 During Pneumonia. Respiratory infection is a leading cause of lung injury and death in the United States. Due to their small size, potentially harmful agents such as bacteria can circumvent initial airway filtration mechanisms, allowing them to invade lower regions of the lung. In response to bacterial colonization, the body mounts an inflammatory response in order to direct the cells of the immune system toward infected airspaces. While this immune response is essential for the clearance of harmful bacteria, it must be precisely regulated in order to prevent lung injury, which can result from excessive inflammation. The researchers will study a protein called signal transducer and activator of transcription-3 (STAT3), which is activated within cells during the immune response to lung infection. The researchers hope to identify factors in the lung that can activate STAT3 and determine the consequence of STAT3 deficiency during bacterial pneumonia. The results of this study will help to identify specific aspects of the immune system response during pneumonia that can be targeted for therapeutic intervention.

RAVIRAJA NEELAVAR SEETHARAM, PhD

Albert Einstein College of Medicine, New York, NY
Research Grant • Funded by the American Lung Association of the City of New York

Studying How "Lung Sweepers" Work To Keep Lungs Free Of Microbes

Determining The Mechanism By Which Axonemal Dynein Arms Effectively Generate Motility. A main function of the respiratory tract is to carry oxygen inhaled as air to red blood cells. Along with air, microorganisms, pollen, and other particulate matter may enter the body. These harmful substances are removed from the respiratory tract by the "mucociliary apparatus," which consists of cells that secrete mucus and are lined with microscopic hair-like structures called cilia. These cells line the upper airways from the nose to the airways deep in the lungs. The cilia beat to sweep mucus and microbes upward and prevent their passage into the lungs. Disease normally occurs when the cilia are defective or compromised so that the mucus is not effectively moved; often the respiratory tract is then colonized with microbes that can destroy the cells. The researchers will study a part of the mucociliary apparatus called dynein arms. This research will provide information that can be used to design treatments for damaged mucociliary apparatus.

CHAD STEELE, PhD

Children's Hospital of Pittsburgh, Pittsburgh, PA
Career Investigator Award • Funded by the American Lung Association

Protecting Against A Deadly Infection In People With Compromised Immune Systems

Dectin-1 And Invasive Pulmonary Aspergillosis. People with defective immune systems are highly susceptible to infection by a variety of organisms, including parasites, bacteria, viruses, and fungi. The fungal organism *Aspergillus fumigatus* is a particular danger to people with compromised immune systems. Current antifungal treatments are not very effective against this severe infection. Many disease-causing organisms, including *A. fumigatus*, enter the body through the lung. Therefore, understanding how the lung immune system works in defending against these organisms is of critical importance. One of the first lung immune cells that a disease-causing organism comes into contact with is the alveolar macrophage. The researchers will investigate a receptor called Dectin-1 on the surface of the alveolar macrophage that recognizes and responds to inhaled *A. fumigatus*. They will also study a new therapeutic

compound based on the structure of Dectin-1 that could enhance the ability of lung immune cells to fight infection caused by *A. fumigatus*.

MINGQUAN ZHENG, MD

Children's Hospital of Pittsburgh, Pittsburgh, PA
Biomedical Research Grant • Funded by the American Lung Association

DNA-Based Influenza Vaccine May Help People With Impaired Immune Systems

CD4-Independent DNA Vaccinations Against Influenza. People with defects in the number and function of infection-fighting white blood cells called T-cells, whether due to HIV infection, cancer, or other diseases that suppress the immune system, are at increased risk from serious influenza. This defect in T-cells impairs both the immune system itself and the effectiveness of the flu vaccine in promoting an immune-system response. The researchers are studying a new DNA-based vaccine in mice with a deficiency in T-cells that protect against influenza. The long-term goal of this research is to develop new DNA vaccine strategies against influenza in patients with AIDS and other conditions that impair the immune system.

LUNG CANCER

Lung cancer kills more men and women than any other form of cancer. We know that cigarette smoking is responsible for most cases, but our ability to treat this disease is woefully inadequate, resulting in a five-year survival rate in approximately 15 percent of patients. The effectiveness of surgery is limited by our inability to detect cancers early enough to cure them. The effectiveness of chemotherapy is limited by its suppression of the immune system, which is vitally needed to control cancer growth and protect against infection. The effectiveness of radiation is limited by its damage to the lungs.

Studies supported by the American Lung Association address these issues by using the techniques of molecular genetics and cell biology to examine how the body regulates lung cancer cell growth, with the hope of defining how it may control cancer at the cellular level. Important new animal models of the especially virulent small cell cancer are being developed. Basic studies are exploring the genetic abnormalities in lung cancer cells, some with a goal of developing novel methods of prevention. Much work is being done at the cellular and molecular levels as unraveling the complex chemistries involved is key to developing new approaches to treatment. Among the new approaches to treatment being investigated are hormone therapy, drugs developed for treatment of arthritis, gene splicing, and the manipulation of the cellular immune system.

American Lung Association Scholar: Lung Cancer



DAVID ROBBINS, PhD
Dartmouth Medical School

When David Robbins, PhD, started his own lab, he wanted to move from studying the basic biology of the protein with the catchy name “hedgehog” to applying this knowledge to the treatment of lung cancer. But he found the transition more difficult than he had originally thought.

But with the help of a Lung Cancer Discovery Award from the American Lung Association, Dr. Robbins, Associate Professor of Pharmacology and Toxicology at Dartmouth Medical School in Hanover, NH, has made progress toward his goal. “Having the Lung Cancer Discovery Award has helped me move my program in the direction I’ve been trying to move it in for the last few years,” he says.

Through his project, “Uncovering Molecular Markers of Hedgehog Antagonist Sensitive Lung Cancer,” Dr. Robbins and his colleague, Dr. Ethan Dimitrovsky, have gained new insight into hedgehog, which is part of a communication network between cells that regulates different genes. “It tells the cells of the tumor to survive,” he says.

Dr. Robbins hopes his work will answer the question of which lung cancer patients will respond to therapy that inhibits hedgehog. This type of therapy is just beginning to be studied in humans. He also hopes to use the research he is doing with the help of his American Lung Association grant to obtain funding from the National Institutes of Health to continue and expand his work.

To see a complete description of Dr. Robbins’ research project, please go to page 45.

ALAN FIELDS, PhD

Mayo Clinic, Jacksonville, FL

Lung Cancer Discovery Award • Funded in partnership between the American Lung Association and the LUNGevery Foundation

Will Arthritis Drug Become An Effective Treatment Against Lung Cancer?

A Novel Small Molecule Inhibitor Of Protein Kinase C Iota For The Treatment Of Lung Cancer. There is an urgent need for new and more effective therapies to treat patients with lung cancer. The researchers have identified a gene called protein kinase C iota (PKCi) that is essential for the development of lung cancer. They have found that the activity of this gene is very high in lung cancers, and that the level of PKCi correlates with poor survival in lung cancer patients. They have found that blocking PKCi activity blocks lung cancer cell growth, suggesting that a drug that blocks PKCi activity might also be an effective treatment against lung cancer. The researchers identified a drug currently being used to treat rheumatoid arthritis that blocks PKCi activity and inhibits lung cancer cell growth. The researchers will investigate which forms of lung cancer are most sensitive to the drug. They will then establish the doses that provide the best anti-tumor activity. Finally they will determine whether the new drug can be given in combination with drugs currently being used to treat lung cancer to increase their effectiveness. Information obtained from this study will be needed in order to begin testing this drug as a new therapy for lung cancer patients.

RANDOLPH HASTINGS, MD, PhD

Veterans Medical Research Foundation, San Diego, CA

Lung Cancer Discovery Award • Funded in partnership between the American Lung Association, the LUNGevery Foundation, and the American Lung Association of California

Hormone Therapy May Slow Growth Of Lung Cancer In Men

Hormonal Therapy For Non-Small Cell Lung Carcinoma. This research will focus on parathyroid hormone-related protein (PTHrP) as a basis for developing new treatments for lung cancer. PTHrP modifies the behavior of many types of cancer and is frequently present in lung cancer. The researchers' previous investigations suggest that PTHrP slows the growth of lung tumors that grow in women and improves survival of women with lung cancer, but not men with the disease. The sex difference may arise because male sex hormones interfere with the beneficial effect of PTHrP

in slowing lung cancer growth. The researchers will investigate whether blocking these hormones could increase the responsiveness of tumors to PTHrP in men and allow the protein to reduce cancer growth, as it does in women. The results of this research could show that treatments already used for prostate cancer are also useful in men with lung cancers that make PTHrP. In women, the PTHrP-based treatment alone may work. The long-term goal is to develop novel therapies for lung cancer and to identify the best groups of patients to receive those therapies.

HASMEENA KATHURIA, MD

Boston University, Boston, MA

Biomedical Research Grant • Co-funded by the American Lung Association and the American Lung Association of New England

Examining Gene's Role In Spread Of Lung Cancer

Molecular Regulation Of Caveolin-1 In Lung Cancer.

In about 75% of patients with lung cancer, tumor cells have already left the original tumor and entered other tissue sites such as lymph nodes by the time the disease is diagnosed. However, little is known about the factors that allow lung tumor cells to leave their original site of formation and move to other tissues and organs. There is some evidence suggesting that the caveolin-1 gene may be involved in several cancer-related processes, particularly those related, to exit from the lung and seeding of cells into other sites. The researchers will study the role of the caveolin-1 gene in this process. This research will provide important new information about the molecular progression of lung tumors and identify new therapeutic targets to block tumor growth and spread.

MATTHEW MEYERSON, MD, PhD

Dana-Farber Cancer Institute, Boston, MA

Career Investigator Award • Funded in partnership between the American Lung Association and the LUNGevery Foundation

Enhancing The Effectiveness Of New Targeted Lung Cancer Drugs

EGFR Pathway Alterations In Human Lung

Adenocarcinomas. The overall five-year survival rate for lung cancer is only 15.5%. The major reason for this is the inadequacy of current chemotherapy treatment. The development of new and effective lung cancer chemotherapy therefore is a major public health imperative. Two new targeted treatments for lung cancer, gefitinib (Iressa) and erlotinib (Tarceva) inhibit the

epidermal growth factor receptor (EGFR) tyrosine kinase, a chemical that is involved in cancer cell growth. These drugs have led to dramatic anti-tumor responses in a fraction of patients with lung adenocarcinoma, the most common form of lung cancer. The researchers have identified frequent mutations in the EGFR gene in lung adenocarcinoma that are associated with sensitivity to these new drugs and appear to explain the rare dramatic responses to them. The researchers hope that their investigations will lead to a better understanding of the role of EGFR in anti-tumor responses that results in improved treatment of lung adenocarcinomas. They also have recently identified EGFR mutations that lead to drug resistance and are seeking ways to overcome this resistance.

TAMARA MINKO, PhD

Rutgers University, Piscataway, NJ
Career Investigator Award • Funded by the American Lung Association of the Mid-Atlantic

Battling Lung Cancer Cells' Resistance To Chemotherapy

Novel Inhalatory Treatment Of Resistant Lung Cancer. Although localized lung tumors can be successfully removed by surgery, the treatment of spreading tumors requires high doses of chemotherapy. However, the effectiveness of chemotherapy is limited by the rapid development of lung tumor resistance. This is caused by mechanisms called “pump” and “nonpump” resistance. Pump resistance is caused by substances called membrane transporters that pump out the anti-cancer agents from cells, decreasing the concentration of the treatment and reducing its effectiveness. The nonpump resistance is an activation of cells' defense against the anticancer drugs, which limits cell death induced by the drugs that penetrate cancer cells. The researchers will investigate whether simultaneously suppressing pump and nonpump resistance will substantially increase the effectiveness of traditional anticancer drugs. Their long-term goal is to develop an inhaled drug delivery system that could be used to treat resistant lung cancer and would significantly increase the effectiveness of chemotherapy for lung cancer, while limiting adverse side effects on healthy tissue.

PHILIPPE MONTGRAIN, MD

University of California, San Diego, San Diego, CA
Senior Research Training Fellowship • Funded by the American Lung Association of California

Male Sex Hormone May Inhibit Protein That Slows Growth Of Lung Cancer

Lung Cancer Suppression By Parathyroid Hormone-Related Protein: Antagonism By Androgens. The researchers have found that a protein called parathyroid hormone-related protein (PTHrP), produced by about two-thirds of lung cancers, slows tumor growth in mice and prolongs survival in humans. This survival benefit is seen only in women, however. The researchers have previously found that tumors in males make less PTHrP than tumors in females. They will study how PTHrP slows lung cancer growth and why the protein's anti-cancer effects depend on gender. They will investigate whether PTHrP decreases the proliferation of tumor cells and whether the male sex hormone testosterone inhibits the production of PTHrP by lung cancer cells, allowing lung tumors in males to make less of the protein and to grow faster. By determining how PTHrP, gender, and hormonal exposure interact to alter lung cancer progression, the researchers hope to advance medical knowledge toward the goal of improved lung cancer therapy.

NOURI NEAMATI, PhD

University of Southern California, Los Angeles, CA
Lung Cancer Discovery Award • Funded in partnership between the American Lung Association and the LUNGevity Foundation

Investigating Novel Treatment For Non-Small Cell Lung Cancer

Preclinical Development of SC21 In Lung Cancer. The overall five-year survival rate from lung cancer diagnosis is 15%. Since many anticancer drugs are not effective against lung cancer, identification of new drugs with novel mechanisms is urgently needed. The researchers are studying a compound called SC21, which they have found in initial tests is a potent fighter against non-small cell lung cancer (NSCLC) cells. Their preliminary tests indicate that SC21 is different in structure and function than any known anticancer drugs. The researchers will carry out an evaluation of SC21 in mouse models and study its optimal dose and safety profile. Information used from this research can be used in designing a Phase I clinical trial of SC21 in lung cancer patients.

KWON-SIK PARK, PhD

Stanford University, Stanford, CA

Senior Research Training Fellowship • Funded by the American Lung Association

Understanding The Origin And Development Of Small Cell Lung Cancer

Mechanisms Of Cancer Initiation In A Mouse Model Of Human Small Cell Lung Carcinoma. The overall five-year survival rate for lung cancer is about 15%; for small cell lung cancer (SCLC), it is only 6%. The high death rate from SCLC is due in part to the fact that only 10-15% of these cancers are detected in the early stages of the disease, making treatment options fewer and less effective. To understand how to improve detection at earlier stages and identify novel treatments, it is critical to understand the basic biology of how SCLC starts and develops. The researchers plan to investigate the molecular and cellular mechanisms of how SCLC begins and develops by studying genetically engineered mice, in which the disease can be induced in a controlled fashion and cancer progression can be monitored. Previous research indicates these mouse tumors are very similar to human SCLCs. A better understanding of the early stages of SCLC will eventually allow researchers to identify markers for SCLC detection and discover novel therapeutic approaches.

DAVID ROBBINS, PhD

Dartmouth Medical School, Hanover, NH

Lung Cancer Discovery Award • Funded in partnership between the American Lung Association and the LUNgevity Foundation with support from Mr. Sylvester F. Minter III

Identifying Which Lung Cancer Patients Are Sensitive To "Hedgehog" Protein

Uncovering Molecular Markers Of Hedgehog Antagonist Sensitive Lung Cancer. There is a pressing need for new lung cancer treatments, given that lung cancer is the leading cause of cancer death in the United States for both men and women. The researchers will study a secreted protein nicknamed Hedgehog, which plays an important role in large numbers of patients with non-small cell lung cancer, the most common type of lung cancer. When the Hedgehog is received, it activates a series of events in the cell, which is referred to as a signal pathway. These events can lead to mutations that result in different types of cancer. The researchers will identify molecular markers that can identify lung cancer that is sensitive to inhibitors of Hedgehog signal activity. These markers would allow doctors to select which lung cancer patients would be most likely to

respond to treatment that targets the Hedgehog signal pathway, maximizing the effectiveness of this novel targeted therapy. The researchers have developed mice that can be used to test Hedgehog pathway antagonists, and treatments that target the Hedgehog pathway. This research has the potential to address the substantial medical need to develop innovative approaches to treat lung cancer.

RAVI SALGIA, MD, PhD

University of Chicago, Chicago, IL

Lung Cancer Discovery Award • Funded in partnership between the American Lung Association, the LUNgevity Foundation, the American Lung Association of the Upper Midwest, and the Myer Family

Stress Proteins: Target For New Lung Cancer Therapy?

Studies And Therapeutic Targeting Of Heat Shock Proteins In Lung Cancer. The need for more effective treatments for lung cancer is obvious, as lung cancer will take the lives of an estimated 160,390 Americans in 2007. The researchers have identified molecules called heat shock proteins (HSPs) to be important in lung cancer. They believe HSPs, especially HSP27, may serve as a novel treatment for lung cancer. HSPs are found in all living organisms. They are also called stress proteins, because they play a central role in the survival of cells under stress and are activated by heat, radiation, and chemotherapy. It has been suggested that cancer cells, unlike normal cells, rely on high concentrations of heat shock proteins to survive. The researchers have begun to evaluate the role of heat shock proteins in lung cancer, and found high amounts of HSP27 in the vast majority of lung tumors. They will study the exact role of HSP27 in lung cancer, which may lead to novel treatments for this devastating disease.

TODD STUKENBERG, PhD

University of Virginia, Charlottesville, VA

Lung Cancer Discovery Award • Funded by the American Lung Association of the Atlantic Coast

Testing Regulator Of Cell Division As Potential Lung Cancer Treatment

Lung Cancer-Promoting Roles Of The Ndc80/Hec1 Kinetochore Complex. All tumors are aneuploid, meaning they have the wrong number of chromosomes. It is believed that this aneuploidy drives the growth of cancer. But it is not known how cells gain and lose chromosomes. Most of this loss and gain of chromosomes occurs during cell division, or mitosis. The researchers

have found that a key regulator of mitosis, called Hec1, is overproduced in most lung cancer cells, and this in turn causes other changes that affect chromosome regulation. The researchers will test whether Hec1 is an important new target for lung cancer therapies.

KOUNOSUKE WATABE, PhD

Southern Illinois University, Springfield, IL

Research Grant • Funded by the American Lung Association of the Upper Midwest

Developing Targeted Lung Cancer Treatment To Avoid Chemotherapy Side Effects

Gene-Specific Silencing For Lung Cancer Therapy.

Despite the high incidence and death rate from lung cancer, there is no effective treatment currently available for patients with advanced disease. Most chemotherapy drugs have strong side effects because they target healthy cells as well as cancer cells, leading to a severely compromised quality of life for the patient. Therefore there is an urgent need to define a specific target molecule in cancer cells in order to develop more effective treatments. The researchers will construct a gene-specific drug for lung cancer by using one of the most current molecular biological techniques. Their long-term goal is to develop a novel therapeutic method by targeting a specific molecule in the tumor cells using a virus-based delivery system that will be inhaled straight into the lungs. They believe that this unique design for lung cancer treatment will eventually yield an effective and non-toxic anticancer drug.

STEPHANIE K. WATKINS, MS

University of Louisville, Louisville, KY

Lung Health Dissertation Grant • Funded by the American Lung Association of the Midland States

Trying To Reverse Lung Cancer's Effect On Immune System Cells

Therapeutic Targeting Of Macrophages Associated With Lung Carcinoma. One of the major ways in which malignant cancer cells evade destruction by the immune system is through the production of molecules that inhibit or prevent immune system responses to the tumor. Macrophages are immune system cells that come into play when tissue is injured. They intensify the number of immune cells entering the injured tissue. They also destroy those areas of tissue harboring invading bacteria and promote the immune system's efforts to destroy the bacteria. Once the bacteria have been destroyed, macrophages begin to inhibit inflammation and mobilization of the immune system, and to promote

wound healing. Malignant tumors attract macrophages and stimulate them to inhibit inflammation and promote tissue growth, thereby helping the tumor grow. The researchers will study whether the effect of the tumor on macrophages is reversible and therefore may be countered by delivering molecules that strongly stimulate the inflammatory activity of macrophages.

YUE XIONG, PhD

University of North Carolina, Chapel Hill, NC

Diane Emdin Sachs Lung Cancer Award • Funded in partnership between the American Lung Association and the American Lung Association of New York State with special thanks to the Emdin Family

Mouse Model Provides Genetic Clues About Small Cell Lung Cancer

Animal Model For Human Small Cell Lung Cancer.

Lung cancer is the leading cause of cancer deaths in the United States for both men and women. Small cell lung cancer (SCLC) accounts for 13% of lung cancers and is highly malignant and aggressive. There is much that is still not known about the molecular mechanism of SCLC. One of the factors slowing down research on this deadly disease is the lack of suitable animal models. Previously, scientists identified alterations in two genes that suppress tumors in humans in SCLC and created mice with these alterations in their lungs. The researchers have identified two more genes, p18 and Men1, which also suppress tumors. They created mice without these two genes, and found these mice developed tumors. They plan to develop a new mouse model with these genetic alterations, in order to find out how these two genes collaborate to suppress SCLC. The model will help researchers better understand SCLC, and provide a suitable animal model for future treatments of lung cancer.

LIN ZHANG, PhD

University of Pittsburgh, Pittsburgh, PA

Career Investigator Award • Funded in partnership between the American Lung Association and the Chest Foundation

Substance That Controls Cell Death May Prove Useful In Lung Cancer Treatment

PUMA As A Novel Sensitizer For The Treatment Of Lung Cancer. The current treatment options for lung cancer patients produce a low rate of response, and virtually no cure. Apoptosis, or programmed cell death, is a normal suicidal process the body uses to selectively remove cells that are no longer needed, damaged, or dangerous. Apoptosis is fundamental to our health;

failure of cells to die leads to initiation and progression of cancer, and makes cancer cells resistant to anticancer drugs. To understand how apoptosis is uncontrolled in cancer cells, the researchers identified PUMA, a novel controller of apoptosis and a target of p53, the gene that is altered in the majority of lung tumors. They found that PUMA is often used by anticancer drugs to kill cancer cells. However, PUMA is frequently interrupted in lung cancer cells due to abnormalities of p53. The researchers aim to use PUMA as a target to encourage selective killing of lung cancer cells. The studies will provide useful information about the molecular mechanisms by which anticancer drugs kill lung cancer cells, and also may provide novel strategies to restore the sensitivity to anticancer therapies in lung cancer cells.

THE IMMUNE SYSTEM, INFLAMMATION, AND LUNG SCARRING

The body defends itself and resists infection by mounting immune (allergic) and inflammatory responses to foreign invaders such as infecting organisms and particulates. Sometimes these defense systems over-respond and identify the body's own molecules as foreign. When the body turns against itself in this way, disease may be created. One example of this is interstitial lung disease or idiopathic pulmonary fibrosis, in which an excessive inflammatory response to seemingly mild stimuli may lead to permanent scarring of the lungs, disability, and death. Because most lung diseases involve inflammation and the cells of the immune system to some degree, the American Lung Association supports an array of investigations into the basic cellular and molecular processes that underlie these systems.

A wide variety of cells, chemical and immunological mediators, involved in inflammation and scarring are being studied, mainly with advanced techniques of molecular genetics. Researchers are also seeking new ways to prevent the lung scarring that follows certain types of lung inflammation, as well as looking for new treatments for lungs damaged by excess scar tissue formation.

New attention is being paid to the basic biology of Lymphangioleiomyomatosis (LAM), an uncommon but potentially deadly disease which primarily affects young women.

American Lung Association Scholar: The Immune System, Inflammation, and Lung Scarring



CHEN DONG, PhD
MD Anderson Cancer Center

When Chen Dong, PhD, was studying the role of a substance called interleukin 17 (IL-17) in autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease, he and his colleagues realized IL-17 also might play a role in lung diseases such as asthma.

They found that mice that produce too much IL-17 in the lung, develop lung inflammation, excess mucus, and changes in the airway. Chronic inflammation is the underlying mechanism for many lung diseases including asthma, COPD, sarcoidosis, and lung cancers.

We became excited about this finding and wished to continue this angle of research,” Dr. Dong says. “The American Lung Association recognized our contribution in this new and evolving area of research, and we’re very grateful for their support. Without this grant, we would not be able to look at IL-17’s role in lung diseases.”

IL-17 is a type of cytokine, which is a protein produced by white blood cells that acts as a chemical messenger between cells. Dr. Dong is studying the white blood cells called T-cells that produce IL-17, called TH-17. “We need to understand what influences these cells to produce IL-17 and other cytokines,” he says. “We hope to understand more about the regulation and function of TH-17 cells and how they contribute to lung inflammation and other kinds of inflammatory diseases.”

Some pharmaceutical companies are already studying antibodies that block IL-17 as potential treatments for autoimmune diseases such as rheumatoid arthritis, Dr. Dong notes. “Once we have more clues about IL-17’s role in lung inflammation, it is possible that these already developed agents could be applied to lung diseases,” he says.

To see a complete description of Dr. Dong’s research project, please go to page 51.

WILLIAM ALTEMEIER, MD

University of Washington, Seattle, WA
Biomedical Research Grant • Support of this grant comes from the Mary Fuller Russell Research Fund

Studying Protein's Role In Acute Lung Injury

Fas-Induced Inflammation: Mechanisms And Role In Acute Lung Injury. Acute lung injury remains a cause of illness and death in the intensive care unit. Despite extensive research efforts, the mechanisms involved in the development of acute lung injury are still not completely understood. Research studies on humans and animal models have identified activation of a protein named Fas as a potentially important mechanism in the development of lung injury and inflammation. The researchers will study the mechanism by which Fas causes inflammation and evaluate the role of inflammation in Fas-induced lung injury. The results of this research will provide new knowledge about how Fas activation contributes to the development of acute lung injury. This will in turn guide future efforts to develop novel therapies effective in preventing acute lung injury.

KAMRAN ATABAI, MD

University of California, San Francisco, San Francisco, CA
Clinical Research Grant • Funded by the American Lung Association of California

Lack Of Protein May Lead To More Severe Lung Scarring After Injury

The Role Of Mfge8 And Apoptotic Cell Clearance In Modulating Pulmonary Fibrosis After Lung Injury. Acute lung injury (ALI) is a common response of the lung to many different types of direct and indirect injury such as pneumonia, multiple bone fractures, and blood transfusions. ALI is characterized by an often escalating spiral of inflammation that can aggravate the lung injury. Despite the same initial degree of injury, some patients recover quickly while others have a progressive and worsening course. When the lung is injured, many cells are killed or undergo programmed cell death, a process called apoptosis in which cells essentially kill themselves when they are under extreme environmental stress. Recent evidence suggests that having too many apoptotic cells in the lung can lead to more severe lung injury and scarring. The researchers will study a protein called Mfge8 that is made in the lung and binds to apoptotic cells, facilitating their removal. They will evaluate whether mice that lack Mfge8 develop more lung scarring after injury. This research has the potential to identify new therapeutic targets for lung injury and scarring.

A. BRENT CARTER, MD

University of Iowa, Iowa City, IA
Career Investigator Award • Funded by the American Lung Association of the Upper Midwest

The Role Of Macrophage Cells In The Development Of Asbestosis

Adequate Levels Of Hydrogen Peroxide Are Necessary For Macrophage Function. Asbestosis, an important cause of pulmonary fibrosis, results from a high occupational exposure to asbestos. Although standards regarding handling asbestos have changed, asbestos-related deaths continue. It is estimated that the number of asbestos-associated deaths in the United States may exceed 200,000 by the year 2030. The lungs of patients with asbestosis contain alveolar macrophages, which are specialized cells that engulf and destroy bacteria and foreign particles in the lungs and other organs. The researchers will study how alveolar macrophages are involved in the development of asbestosis. The findings will apply not only to asbestosis, but also to other lung diseases, and may be helpful in the development of treatments to limit lung injury and pulmonary fibrosis.

CHEN DONG, PhD

University of Texas MD Anderson Cancer Center, Houston, TX
John L. Kirkwood Career Investigator Award • Funded by the American Lung Association

Better Understanding Of Lung Inflammation May Shed Light On Many Lung Diseases

Lung Inflammation Mediated By Inflammatory Helper T-Cells. Chronic inflammation is the underlying mechanism for many lung diseases including asthma, COPD, sarcoidosis, and lung cancers. Development of lung inflammation is complex. The researchers are studying a type of cell that produces a substance called interleukin-17, or IL-17, which has been associated with asthma. They have found that mice that produce too much IL-17 in the lung developed lung inflammation, excess mucus, and changes in the airway. The researchers will study the regulation and function of white blood cells called T-cells that produce IL-17 during lung inflammation. The research will provide new explanations of the mechanisms in the development of lung disease and may suggest new treatment.

PATRICIA DUBIN, MD

Children's Hospital of Pittsburgh, Pittsburgh, PA
Biomedical Research Grant • Support of this grant comes from the Mary Fuller Russell Research Fund

Seeking Key To Immune System's Response To Deadly Pneumonia Bacteria

IL-23 And Pseudomonas Aeruginosa Pneumonia. The bacterium *Pseudomonas aeruginosa* causes pneumonia in individuals who are on a ventilator, as well as people whose immune systems are compromised due to cystic fibrosis, AIDS, low birth weight, or other causes. Some studies show that when *P. aeruginosa* infection spreads from the initial site of infection, through the bloodstream, more than 50% of the infected individuals will die. In spite of many advances in medical care, this figure has not improved in the last 20 years. Though *P. aeruginosa* is often blamed for the significant lung damage associated with infection, the immune system is also responsible. The researchers will study IL-23, a molecule produced by the immune cells that first recognize *P. aeruginosa* in the lung. Understanding the mechanism of IL-23 will provide significant insight into the immune system's response to *P. aeruginosa*. This knowledge will lay the groundwork for ultimately developing the treatments against *P. aeruginosa* infection, allowing doctors to prevent, rather than respond to, lung damage and subsequent illness.

MONICA FOOTE, PhD

Cornell University, Ithaca, NY
Senior Research Training Fellowship • Funded by the American Lung Association

Understanding Immune Helper Cells May Lead To Better Treatment For Allergic Asthma

Epigenetic Regulation Of The Neonatal Th2 Bias. Allergic diseases, including asthma, are inflammatory disorders that result when the immune system mounts an irregular response to environmental allergens. It is estimated that half of Americans with asthma suffer from allergic asthma, a condition that is commonly believed to originate in neonatal or fetal life. Certain white blood cells, called T helper (Th) cells, help other immune cells to mount responses by producing and secreting immune growth factors called cytokines. The immune system produces Th1 and Th2 cells, and both are needed for an effective immune response. People susceptible to allergic asthma, however, often mount potent Th2 responses. The researchers will investigate the mechanisms governing the development and persistence of early-life Th2 function, which will provide

information that will be valuable in developing targeted, safe, and effective treatments for allergic asthma in children.

MARILYN GLASSBERG, MD

University of Miami, Miami, FL
Career Investigator • Funded by the American Lung Association of Florida

Searching For New Targets For Treatment Of Rare Women's Lung Disease

New Directions In The Treatment Of Lymphangioliomyomatosis. Lymphangioliomyomatosis, or LAM, is an aggressive, destructive, and eventually fatal lung disease of women. In this rare disease an unusual type of muscle cell invades the lungs, forming bundles that grow into the walls of the airways and form cysts that completely destroy the lungs. Increased activity of enzymes in the lung called matrix metalloproteinases (MMPs) may be involved in LAM. In addition, female sex hormones, particularly estrogen, have been implicated in LAM, since the disease occurs only in women and is predominantly diagnosed during their reproductive years. The researchers will study molecules that inhibit MMPs that are fueled by estrogen. The results of the study could help tailor new therapies for the successful treatment of LAM.

QIHAI GU, MD

University of Kentucky, Lexington, KY
Biomedical Research Grant • Co-funded by the American Lung Association and the American Lung Association of the Midland States

Determining A Chemical's Role In Airway Inflammation

Protease-Activated Receptor-2 And Pulmonary C-Neuron Hypersensitivity. A chemical called protease-activated receptor-2 (PAR2) is produced in various cells in the airways and lungs, and contributes to airway inflammation and airway hyperresponsiveness — two prominent features of many respiratory diseases such as asthma. The researchers plan to uncover the mechanisms underlying the potent actions of PAR2 in the airways, and the relationship between PAR2 and sensory nerves in the airways. The insights gained from this research may be valuable in developing new therapeutic strategies for the treatment of airway inflammatory diseases, including asthma.

SUSANNA HARJU, PhD

University of Washington, Seattle, WA
Senior Research Training Fellowship • Funded by the
 American Lung Association of the Northwest

Understanding How The Lung Protects Itself Against Noxious Agents

Role Of Matrilysin-Mediated E-Cadherin Shedding In Wound Healing. The epithelium is a layer of cells that protects the lungs against toxins, pollutants, and infectious agents, and initiates the body's inflammatory responses if the lungs are injured. Epithelial cells are tightly joined and establish a nearly impassable barrier to bacteria. Upon injury, these cells begin a series of responses to heal wounded tissue. It is likely that the lung's epithelial cells are constantly being subjected to minor injuries. The ability of these tissues to rapidly and efficiently repair these wounds is essential to restoring the barrier function of the epithelium, and preventing the establishment of infection. The epithelium is chronically disrupted in a variety of lung conditions, such as COPD, cystic fibrosis, asthma, and cancer. The researchers will study two proteins, matrilysin (MMP-7) and E-cadherin, which are involved in wound repair in the lungs. Their study will contribute to a better understanding of the fundamental repair mechanisms of lung epithelium.

JEFFREY HOROWITZ, MD

University of Michigan, Ann Arbor, MI
Dalsemer Research Grant • Funded by the American Lung
 Association

**Blocking A Chemical Messenger That Promotes Scarring In
 Pulmonary Fibrosis**

Mesenchymal Cell Survival Signaling In The Pathogenesis Of Pulmonary Fibrosis. Idiopathic pulmonary fibrosis is a chronic, progressive, debilitating lung disease with a high mortality rate and no effective treatments. The cause of the disease is not known, but it is thought that it involves an abnormal wound repair response to an unidentified lung injury. Myofibroblasts are cells that are important in normal wound-repair responses. In Idiopathic Pulmonary Fibrosis, however, myofibroblasts abnormally accumulate near the areas of lung injury. A chemical messenger called transforming growth factor-beta 1 (TGF-beta1) leads to the activation of myofibroblasts and their overproduction of scar-causing proteins. TGF-beta1 seems to inappropriately protect myofibroblasts from programmed cell death, thereby continuing the process of scarring in the lungs. The researchers hope to gain a better understanding of how this process happens, so that they can block the

detrimental effects of TGF-beta1 while preserving other beneficial effects of TGF-beta1 in other types of cells. The study will identify novel approaches to treating pulmonary fibrosis and preventing progression of this disease.

SAMITHAMBY JEYASEELAN, DVM, PhD

National Jewish Medical and Research Center, Denver, CO
Biomedical Research Grant • Support of this grant comes
 from the Mary Fuller Russell Research Fund

**Gaining Insight Into Immune System's Response To Bacteria During
 Pneumonia**

Pulmonary Innate Defense Against Vacuolar Pathogens Using Legionella Pneumophila As A Model. Each year, bacterial pneumonia affects more than one million adults in the United States, and causes 30,000 deaths. Although some advances have been made in the recent past in understanding bacterial pneumonia, there are still no effective control measures. The majority of bacterial pneumonia is caused by germs that live and multiply in a structure inside cells called vacuoles. The researchers will explore the immune system's response to these vacuole-enclosed bacteria using *Legionella pneumophila* as a model. They will focus on recently discovered receptors called toll-like receptors, or TLRs, which sense the presence of germs and trigger a cascade of signals in immune cells. These signals lead to the body's immune system responses, which help eliminate the intruding germs. There is an immediate need for a safe and efficient vaccine to control pneumonia germs that cause devastating lung disease. Understanding how to manipulate the body's immune response to these germs could provide an important target for the development of an efficient vaccine against pneumonia without adverse side effects.

VERA P. KRYMSKAYA, PhD

University of Pennsylvania, Philadelphia, PA
Career Investigator Award • Funded in partnership between
 the American Lung Association and the LAM Foundation

**Tumor Suppressor Gene May Hold Key To Cell Growth In Lung
 Disease**

Mechanisms Regulating Cell Migration In Lymphangiomyomatosis. Lymphangiomyomatosis (LAM) is a rare genetic disorder of unknown origin primarily affecting women of childbearing age. LAM is characterized by the unusual growth of smooth muscle cells in the interstitium (the supportive tissue between the air sacs of the lungs). These smooth muscle cells invade the tissue of the lungs, including

the airways and blood and lymph vessels. This cell migration disrupts the normal lung structure and leads to lung damage and death. A connection has been found between LAM and the loss of function or mutation of the tumor suppressor gene TSC2. The researchers have found that “turning on” this gene can stop the LAM cell migration. They are studying the mechanisms by which TSC2 regulates LAM cell invasive growth. Insight into the role of TSC2 in LAM pathobiology would advance the development of therapeutic strategies to treat the disease. The findings also may have implications for other lung diseases such as asthma, idiopathic pulmonary fibrosis, or interstitial lung disease.

SAMIR MAKANI, MD

University of California, San Diego, San Diego, CA
Junior Research Training Fellowship • Funded by the American Lung Association of California

Understanding The Immune System’s Role In Asthma

The Role Of Toll-Like Receptor 2 In Allergic

Inflammation. The immune system plays an important role in asthma, but much of its function in asthma is still not understood. The immune system has two major parts, the innate immune system and the adaptive immune system. The innate immune system is our first line of defense against invading organisms while the adaptive immune system acts as a second line of defense and also affords protection against re-exposure to the same pathogen. Recent data suggests the importance of the innate immune response in allergic inflammation. The researchers will study the innate immune system’s role in asthma, focusing on toll-like receptors (TLRs), located on cells of the innate immune system. The researchers hope to provide information that can be used to develop new therapeutic targets for asthma that prevent or modify the initial steps that lead to the cascade of events that end in an asthma attack.

BETHANY B. MOORE, PhD

University of Michigan, Ann Arbor, MI
Career Investigator Award • Funded by the American Lung Association of the Midland States

Seeking Way To Block Development Of Pulmonary Fibrosis

Recruitment And Activation Of Lung Fibrocytes In Experimental Pulmonary Fibrosis. Idiopathic pulmonary fibrosis (IPF) is a progressive and devastating disease that results from the accumulation of scar tissue in the lung. Unfortunately, standard treatment options have been disappointing. A better understanding of the

development of IPF is necessary before new treatment options can be identified and tested. The researchers previously found that the process of fibrosis (scarring) depends on the presence of a certain cell surface molecule called the CCR2 chemokine receptor. This receptor is like a lock into which fit certain chemical chemokine keys that are responsible for the migration of infection-fighting cells to sites of infection or inflammation in the body. The researchers have found that mice that do not have this receptor do not develop fibrosis. They will now study the mechanism through which these mice are protected from fibrosis. The researchers believe that a unique population of circulating cells called fibrocytes that express the CCR2 chemokine receptor gets recruited to the lung during fibrosis. Once there, these fibrocyte cells can speed up the fibrotic process. If the researchers can prove that these receptors and/or these fibrocytes are critical to the development of the disease, then they can focus efforts on blocking the receptors (thereby blocking fibrocyte recruitment to the lung) to provide a new therapy which may limit or prevent progression of pulmonary fibrosis.

KAREN L. OSLUND, DVM, PhD

University of California, Davis, Davis, CA
Research Grant • Funded by the American Lung Association of California

How Does Protein Protect Airway Cells From Injury From Harmful Pollutants?

Role Of Thioredoxin In Airway Epithelial Oxidant

Injury. The lungs are subjected to insults daily, including exposure to tobacco smoke and air pollutants such as ozone. The cells lining the airways must develop defenses to guard against this injury. The researchers will be studying thioredoxin, a protein found in cells lining the airways, which is produced after exposure to these injurious substances. Thioredoxin acts to protect cells from injury and also helps to incite an inflammatory response after there is an injury. Specifically, the researchers will investigate whether thioredoxin is produced in response to exposure to ozone or tobacco smoke, and if so, if it protects the cells from further injury. The researchers will also examine whether airway lining cells that produce a large amount of thioredoxin are more resistant to injury after exposure to ozone or tobacco smoke. Finally, they will look at the protein’s role in beginning an inflammatory response after an injury to the airway cells.

LEE QUINTON, PhD

Harvard University School of Public Health, Boston, MA
Senior Research Training Fellowship • Co-funded by
 the American Lung Association and the American Lung
 Association of New England

Targeting The Immune System's Response To Bacterial Pneumonia

IL-6 Family Cytokines And Alveolar Epithelial STAT3 During Pneumonia. Respiratory infection is a leading cause of lung injury and death in the United States. Due to their small size, potentially harmful agents such as bacteria can circumvent initial airway filtration mechanisms, allowing them to invade lower regions of the lung. In response to bacterial colonization, the body mounts an inflammatory response in order to direct the cells of the immune system toward infected airspaces. While this immune response is essential for the clearance of harmful bacteria, it must be precisely regulated in order to prevent lung injury, which can result from excessive inflammation. The researchers will study a protein called signal transducer and activator of transcription-3 (STAT3) which is activated within cells during the immune response to lung infection. The researchers hope to identify factors in the lung that can activate STAT3 and determine the consequence of STAT3 deficiency during bacterial pneumonia. The results of this study will help to identify specific aspects of the immune system response during pneumonia that can be targeted for therapeutic intervention.

PING-HUI TSENG, PhD

University of California, San Diego, San Diego, CA
Junior Research Training Fellowship • Funded by the
 American Lung Association of California

Unraveling The Protective And Destructive Roles Of Immune Cell Receptors

Developing Peptide Inhibitors Targeting Different Components Of Toll-Like Receptors (TLRs) Signaling Pathways. Toll-like receptors (TLRs) are proteins of immune cells that serve as a key part of the innate immune system, which recognizes infectious threats. When TLRs are activated, the immune system responds to these threats. TLRs are involved in many lung diseases such as asthma, acute respiratory distress syndrome, and lung cancer. In addition to their protective function, TLRs can also cause damage, for reasons that are not understood. The researchers will try to develop a novel tool that can improve understanding of how TLR proteins communicate, and how this impacts lung health. This tool could allow for development of new therapeutic approaches that could selectively block un-

desired TLR-triggered responses without affecting the protein's beneficial responses for lung diseases.

GARETH WALLIS, PhD

University of California, Berkeley, Berkeley, CA
Senior Research Training Fellowship • Funded by the
 American Lung Association

Revealing The Lung's Role In Metabolism In Response To Stressful Situations

The Lung As A Fulcrum Of Metabolic Integration. The lung's activities extend far beyond the exchange of gases. The lung is also a metabolic organ, meaning it is involved in the use and production of various fuel sources. Normally, glucose is the major fuel used by lung tissue for energy, but the lung can also take up and use the end products of glucose metabolism. Scientists still have limited information about the metabolic roles of the lung, particularly in response to stressful situations (such as exercise or disease). The researchers will study the metabolic roles of the lung in a rat model. They will take samples of blood entering and leaving the lungs at rest and in response to interventions that will simulate the metabolic demands placed on the body by physical exercise. These studies aim to demonstrate previously unknown metabolic activities of the lung and identify the cell types and mechanisms involved. Furthering the fundamental knowledge of lung metabolism may reveal important implications for understanding metabolic disturbances associated with diseases of the respiratory and other body systems.

EUN JUN YUN, PhD

University of California, San Francisco, San Francisco, CA
Senior Research Training Fellowship • Funded by the
 American Lung Association of the Upper Midwest and the
 Alpha-1 Foundation

Connective Tissue Cell Research May Hold Promise For Pulmonary Fibrosis

The Regulation Of Myofibroblast Development And Apoptosis. Myofibroblasts are connective tissue cells that play an important role in the development of the air sacs in the lungs, called alveoli. The mechanisms that regulate myofibroblast development are not fully understood. Disrupted lung myofibroblast development may lead to lung disorders such as bronchopulmonary dysplasia, pulmonary fibrosis (scarring), and emphysema. Therefore, it is important to understand the development and maintenance of this cell type. The researchers will test whether the balance between myofibroblast devel-

opment and death is necessary for both the formation of alveoli in the developing lungs and the maintenance and repair of alveoli in adult lungs. Based on previous research, the scientists predict that two growth factors (types of protein) work to regulate myofibroblast balance. They will use genetically modified mice to study the function of these growth factors on myofibroblast development. The results obtained from these studies will further the understanding of the mechanisms of lung formation and of the development of lung fibrosis, and may provide novel targets for the development of new antifibrotic therapies.

DISEASES OF INFANTS AND CHILDREN

Research supported by the American Lung Association has contributed significantly to scientific progress in understanding and treating respiratory disorders of infants and children. Deaths of premature infants due to respiratory distress syndrome (RDS) have decreased dramatically over the past 30 years, thanks to more sophisticated care and modern medicine's ability to replace a critical molecule called surfactant that is absent in premature lungs. Improved care techniques can now prolong life in children with cystic fibrosis (CF). A clearer understanding of infant breathing has led to practical measures that have reduced deaths from sudden infant death syndrome (SIDS), or crib death.

Despite these advances, lung diseases and breathing disorders remain leading causes of death in infants up to one year of age. There is still no cure for cystic fibrosis, and the problems of treatment have increased as people with this condition live longer. New technologies allow delivery of more and more premature infants at risk for RDS. Many of those who survive develop a chronic illness called bronchopulmonary dysplasia, which is caused by the excess oxygen used to support life in these fragile infants. More than 75,000 to 125,000 children are hospitalized each year due to respiratory syncytial virus (RSV), and an estimated 2% of them die of complications related to the disease.

Research supported by American Lung Association investigators this year will examine the process of lung development in order to understand the challenges of the lungs of premature infants. In addition, the mechanisms of lung injury produced by vital but potentially toxic oxygen therapy of premature infants will be studied.

American Lung Association Scholar: Diseases of Infants and Children



CHRISTOPHER M. EVANS, PhD. MD
MD Anderson Cancer Center

For the past year, Christopher M. Evans, PhD, has been studying the effects of mucus secretion on airflow in the lungs with a research grant from the American Lung Association. When the airways become blocked with too much mucus, resulting from mucus overproduction, the risk of disease worsening or death increases in people with asthma, chronic obstructive pulmonary disease, and cystic fibrosis.

The researchers have identified two major genes called Muc5ac and Muc5b mucins in the airways that produce mucus. Under healthy conditions, Muc5b is abundant and Muc5ac is scant. During inflammation, Muc5ac production increases dramatically. When hydrated, mucus spreads and becomes very thick. This results in mucus plugs that completely block the airway, which can result in fatal asthma. It is thought that Muc5ac is responsible for this. “Proteins that cause the hypersecretion of mucus are therefore important therapeutic targets. Knocking out disease state mucins may fully reverse the lethal component of fatal asthma,” Dr. Evans says.

Dr. Evans is investigating the influence of mucus secretion on airway obstruction by examining what happens when its key components are added or taken away from the lung. His lab has generated mice that can overproduce mucins in the airways and mice that have no Muc5ac or Muc5b in the airways. He has established a method for measuring the effects of mucus secretion on airflow, and has generated a significant amount of information on the effects of mucus production on the airways.

“The American Lung Association grant has given me the time and money I need to gather preliminary data to apply for a larger National Institutes of Health grant,” he says.

To see a complete description of Dr. Evans’ research project, please go to page 26.

PAO-TIEN CHUANG, MD, PhD

University of California, San Francisco, San Francisco, CA
Career Investigator Award • Funded by the American Lung Association

Signal Between Types Of Lung Cells May Provide Clues To Lung Development

Fu And Sufu Function Through Different Types Of Cilia In Controlling Lung Development And Function. Proper lung function in adults relies on normal embryonic development. In lung development, a tube-like structure undergoes extensive branching to generate an elaborate respiratory tree that is essential for gas exchange after birth. This structure is comprised of a layer of cells called epithelial cells. Instructive signals for epithelial branching live in a surrounding tissue layer called the mesenchyme. The researchers will use mouse lungs to understand how a secreted protein called the Hedgehog mediates between the epithelial cells and the mesenchyme and regulates their development. When the Hedgehog is received, it activates a series of events in the cell, which is referred to as a signaling pathway. Major signaling pathways including the Hedgehog pathway are thought to control cell proliferation and differentiation as well as stem cell maintenance and cancer formation. This research will lead to a better understanding of the molecular basis of lung development. It also may shed light on the molecular mechanisms of lung cancers and provide cell-based therapy for lung diseases using stem cells. The researchers also will study the link between Hedgehog signaling and cilia, hair-like structures that line the airways and help to clean them out. Their studies will help increase understanding of diseases related to defective cilia, including bronchiectasis and sinusitis.

XANTHI COUROUCLI, MD

Baylor College of Medicine, Houston, TX
Research Grant • Funded by the American Lung Association of the Central States

Protecting Premature Babies' Lungs Against Damage From Oxygen Therapy

Role Of Cytochrome P4501A Enzymes In Hyperoxia-Induced Lung Injury In The Newborn. Therapy with supplemental oxygen is frequently used in preterm and full-term infants and in adults with acute respiratory distress syndrome (ARDS). Every year, about 70,000 newborns in the U.S. experience breathing problems, which if severe, will require high concentrations of supplemental oxygen and mechanical ventilation. While oxygen therapy may be life-sustaining, it may also injure

the lung. Considerable evidence links too much oxygen to the development of bronchopulmonary dysplasia (BPD), the major source of illness and death in premature infants. The molecular mechanisms responsible for oxygen-caused damage are not completely understood. The researchers will investigate whether enzymes called P450 (CYP)1A play a protective role against lung injury caused by oxygen. This research should provide critical information that can be used to develop novel strategies for the prevention and treatment of BPD associated with excessive oxygen exposures in premature infants.

NEVIS FREGIEN, PhD

University of Miami, Miami, FL
Career Investigator • Funded by the American Lung Association of Florida

Balancing Cells That Produce And Clear Mucus From The Airways

Molecular Regulation Of The Foxj1 Gene, Control Of Ciliated Epithelial Cell Differentiation. The airways are lined with a layer of many different types of cells known collectively as the epithelial layer. These cells play a major role in protecting the lungs from toxic substances that might be inhaled during breathing. Among these cells are those that secrete the substances that make up much of the sticky, viscous mucus that covers the epithelial lining and entrap particles and other potentially harmful substances that enter the airway. There are also cells that have multiple finger-like appendages on their surfaces, called cilia, that move in a wave along the top of the epithelium and propel the toxin-containing mucus upward and out of the airway. Proper regulation of the number of these cell types is critical for normal airway function. For instance, if there are too few cilia cells and too many mucus-producing cells, mucus will not be properly cleared from the airways. The researchers will study how cells in the developing embryonic lung become either cilia cells or mucus-producing cells. The findings may provide new approaches to treating lung diseases that involve loss of cilia cells, such as cystic fibrosis.

DANNY HSIA, MD

University of Washington, Seattle, WA
Junior Research Training Fellowship • Funded by the American Lung Association of the Northwest

Predicting Which Children With RSV Will Develop Asthma

Exhaled Nitric Oxide Output In Infants With Pulmonary Hyperinflation Following Respiratory Syncytial Virus Bronchiolitis. Most lower respiratory tract illnesses with wheezing that occur in the first three years of life are associated with infection with respiratory syncytial virus (RSV). Many studies have shown an association between RSV, subsequent wheezing, and the development of asthma. Between 20-40% of young children who have RSV suffer from recurrent wheezing episodes that resolve on their own as the child gets older. A major challenge for doctors is predicting which infants are at increased risk for developing asthma after RSV and which will resolve on their own. The researchers will use two measurements to see how each alone and in combination predicts recurrent wheezing as the child grows. One measurement, called the thoracic index, measures persistent airway narrowing, while the nitric oxide index measures ongoing airway inflammation. If these measurements prove useful, they will allow doctors to identify which children who have had RSV might benefit from asthma therapy very early in life and avoid complications of asthma in very young children.

ANNE MOON, MD, PhD

University of Utah, Salt Lake City, UT
Career Investigator Award • Co-Funded by the American Lung Association and the American Lung Association of the Southwest

Growth Factor That Stimulates Air Sac Development May Help Premature Babies

A Novel And Required Role For Fgf8 In Pulmonary Development. The researchers will investigate a critical but previously unknown role for a molecule called Fibroblast Growth Factor 8 (Fgf8) in the formation of the tiny air sacs in the lungs, called alveoli. Using a mouse model, the researchers hope to define the role(s) of Fgf8 during lung development. Alveolar underdevelopment is a common, frequently deadly complication of premature birth and of other poorly understood conditions present at birth. The alveolar phase of lung development normally begins in the final months of fetal development and continues after birth; disruption of early alveolar formation impacts lung development both before and after birth. It also impacts lung function and ultimately, survival. In spite of treatment for this con-

dition, the rate of early death and long-term illness in affected infants is high. Even in babies born full-term, alveolar underdevelopment and abnormal development are serious immediate threats to life and cause long-term illness. If the researchers can identify a growth factor that stimulates normal alveolar development, this could represent a major development for treatment of infants with this condition.

NGUYET NGUYEN, MD

Washington University, St. Louis, MO
Research Grant • Funded by the American Lung Association of the Central States

Uncovering Key Process in Abnormal Lung Development

Laminin Alpha5 And Distal Lung Epithelial Cell Differentiation And Function. Laminins are a major component of basement membranes, which are thin layers of tissue that sit under and surround cells of many organs. Basement membranes have been shown to affect the cells that sit on them, particularly during development and sometimes during repair after injury. Every laminin has various chains, which can differ in different tissues. The researchers are focusing on the laminin alpha5 chain. Mutant mice that cannot make laminin alpha5 in lung airway cells have defective lungs. They die soon after birth from breathing problems. Epithelial cells, which line the airways of the lungs, do not develop properly in mutant mice so they do not make at least one ingredient that is key for forming normal lungs. It is not known how this process occurs. The researchers will study laminin alpha5 and epithelial cell surface molecules in the lung. The research will help to determine which laminin alpha5 and lung epithelial cell surface molecule interactions are needed for the cell to stay a normal lung epithelial cell. The findings will have implications for understanding lung development.

TERESA E. WAGNER, MD

University of Washington, Seattle, WA
Senior Research Training Fellowship • Funded by the American Lung Association of the Northwest

Seeking Better Understanding Of Lung Development May Help Premature Newborns

Mechanisms Of Alveolar Septation. Little is known about how normal alveoli, or the lung's air sacs, develop. Alveoli are formed primarily after birth up until 18 months of age. This can be disrupted by premature birth, infection, mechanical ventilation, or too much or too little oxygen, resulting in a lung disease called

bronchopulmonary dysplasia, which involves impaired formation of the alveoli. The researchers hope to gain a better understanding of how alveoli develop in the lung after birth, a process called alveolar septation. A better understanding of the molecular processes involved in alveolar development can lead to preventive and/or therapeutic measures in caring for premature newborns.

SLEEP DISORDERED BREATHING

We all know people who snore and usually consider it an annoyance rather than a problem. However, some people who snore actually stop breathing many times during the night and develop a serious condition called sleep apnea. The most common form of therapy involves the use of a special device which keeps the upper airway open during sleep.

This year, the American Lung Association will support studies which are designed to make the use of this device more comfortable. Studies will also examine the relationship of this relatively common disorder to heart disease.

American Lung Association Scholar: Sleep Disordered Breathing



SANJA JELIC, MD
Columbia University Medical Center

Obstructive sleep apnea (OSA) can lead to high blood pressure, heart failure, and stroke, but scientists do not have a clear understanding of the underlying link between sleep apnea and cardiovascular disease. Sanja Jelic, MD, is using an American Lung Association research grant to investigate this connection.

“The decrease in oxygen levels in the blood may negatively affect the blood vessels and the cardiovascular system,” Dr. Jelic says. She has found that in people with obstructive sleep apnea, the cells lining the blood vessel walls—the first line of defense that senses low oxygen levels in blood—respond in a way that’s commonly seen in the beginning of heart disease. “We see these changes in people with sleep apnea who don’t have obvious heart or blood vessel disease,” she says.

She will investigate whether treatment with continuous positive airway pressure (CPAP), the most common treatment for OSA, restores normal blood vessel wall function in patients with sleep apnea. “If you can find people with sleep apnea early and treat them with CPAP, they may never develop heart disease, or it may at least be delayed,” she says.

“The American Lung Association grant has enabled me to take the seed of an idea and expand it. Without the grant, I would not have been able to do this project,” Dr. Jelic says. She is hoping to use the findings of this 70-person study to find funding so that she can run a larger multicenter trial.

To see a complete description of Dr. Jelic’s research project, please go to page 65.

SANJA JELIC, MD

Columbia University Medical Center, New York, NY
Clinical Patient Care Research Grant • Funded by the
American Lung Association

**Targeting Link Between Sleep Apnea And Heart Disease May Yield
New Treatments**

Targeting Endothelial Dysfunction In Sleep Apnea.

Untreated obstructive sleep apnea (OSA) causes excessive daytime sleepiness, which results in increased risk of accidents at work and while driving. OSA has been linked to high blood pressure, heart failure, stroke, and increased risk of death. However, the mechanism underlying the association between OSA and heart disease is not well understood. Patients with OSA experience repetitive low blood oxygen levels while asleep, resulting in increased blood vessel wall stiffness. Repetitive decrease in blood oxygen levels causes increased production of toxic substances that can damage blood vessel walls and ultimately lead to development of heart disease. The researchers will study the molecular mechanism of abnormal blood vessel wall function and determine whether and how treatment with continuous positive airway pressure (CPAP), the most common treatment for OSA, restores normal blood vessel wall function in patients with sleep apnea. This information will help explain why OSA patients have a higher incidence of heart disease and whether treatment with CPAP reduces their risk for heart complications. This may help to identify new treatment strategies for OSA that would target specific molecular abnormalities and further reduce the risk of heart disease in these patients.

VIJAY SEELALL, MD

New York University, New York, NY
Research Grant • Funded by the American Lung Association
of the City of New York

Making CPAP More Comfortable For Some Sleep Apnea Patients

***Effect Of Nasal Resistance On Delivered Continuous
Positive Airway Pressure In The Treatment Of***

Obstructive Sleep Apnea. Obstructive sleep apnea, in addition to causing daytime sleepiness, also is associated with high blood pressure, heart disease, stroke, and sudden death. The most effective treatment for sleep apnea is an apparatus called nasal CPAP (continuous positive airway pressure), which delivers air through a mask while the patient sleeps, keeping the airway open. However despite the benefits of CPAP, many patients do not use it as prescribed. One patient complaint is that it is difficult to breathe out while on CPAP. Compliance is even more of an issue in patients with high nasal resistance, which is increased difficulty getting air through the passages of the nose because of blockage (i.e., a stuffy nose). Compliance may be improved with flexible CPAP, a device that lowers exhalation pressure, making it easier for the patient to breathe out. The researchers will study the mechanisms that may make CPAP more difficult to use in patients with high nasal resistance and evaluate the changes in pressure that flexible CPAP can provide. The ability to be able to predict who will benefit from flexible CPAP based on a measurement of nasal resistance could help target the therapy and improve compliance in these patients.

GLOSSARY

acute

A condition that progresses quickly and continues for a short time.

adenovirus

One of a group of viruses causing upper respiratory disease, including colds.

AIDS

(Acquired Immunodeficiency Syndrome) A disease in which the cellular immune system is disabled. It is caused by infection by the human immunodeficiency virus (HIV). HIV destroys a specific white blood cell, the helper T-lymphocyte or T-cell. Without this T-cell, the cellular immune system cannot function properly. AIDS is diagnosed in a patient with HIV infection who has a major complication, such as *pneumocystis carinii pneumonia*.

airway

The route for passage of air into and out of the lung.

allele

Mutually exclusive forms of the same gene, occupying the same locus on homologous chromosomes, and governing the same biochemical and developmental process.

allergen

A substance capable of inducing allergy or specific hypersensitivity, such as pollen.

alveolar

Relating to the alveolus (singular) or alveoli (plural), the terminal, tiny saclike structures in the lung where gas exchange takes place.

amoeba

A genus of naked, lobose, pseudopod-forming protozoa of the class Sarcodina that are abundant soil-dwellers, especially in rich organic debris, and are also commonly found as parasites.

angiogenesis

The formation and differentiation of blood vessels.

antigen

Any molecule that provokes the synthesis of an antibody.

antioxidant

A substance that hinders oxidation. In the lung, oxidant molecules are suspected of contributing to a variety of serious conditions; antioxidants can be an important defense.

apoptosis

A genetically determined process of cell self-destruction, that is marked by the fragmentation of nuclear DNA, is activated either by the presence of a stimulus or by the removal of a stimulus or suppressing agent is a normal physiological process eliminating DNA-damaged, superfluous, or unwanted cells (as immune cells targeted against the self in the development of self-tolerance or

larval cells in amphibians undergoing metamorphosis); and when halted (as by genetic mutation) may result in uncontrolled cell growth and tumor formation.

asbestosis

A disease in which the lungs become scarred with fibrous tissue. It results from a high occupational exposure to asbestos.

aspergillus

A genus of fungi with black, brown, or green spores that includes many common molds such as *clavatus*, *flavus*, *aspergillus fumigatus*, *nidulans*, *niger*, and *tereus*.

asthma

A syndrome caused by chronic inflammation of the airway canal, characterized by increased reactivity of the airways to a variety of stimuli, which results in reversible airway swelling, spasm, and increased mucus production characterized by cough, wheezing, and shortness of breath.

autoimmune disease

A disease that results when the immune system attacks elements of its own body.

bacteremia

The usually transient presence of bacteria in the blood.

bacterium

(Bacteria) A single-celled, microscopic organism existing in many forms, some of which cause disease.

beta-adrenergic agonists

Any of various drugs that combine with and activate receptors which exist on cell surfaces of some effector organs and tissues, explains the specificity of certain adrenergic agents in activating or blocking only some sympathetic activities (as vasodilation, increase in muscular contraction and beat of the heart, and relaxation of smooth muscle in the bronchi and intestine).

biochemistry

The chemistry of living organisms.

BPD

(Bronchopulmonary Dysplasia) A condition of the lungs in infants and children which may follow the treatment of respiratory distress syndrome in infants. It is characterized by distortion of the airways and scar formation.

bronchiectasis

A chronic inflammatory or degenerative condition of one or more bronchi or bronchioles marked by dilatation and loss of elasticity of the walls.

bronchiolitis obliterans

Extensive scarring (fibrosis) of the small airways.

bronchitis

Inflammation of the bronchial tubes.

bronchoconstriction

Reduction in the caliber of a bronchus or bronchi.

calcium channels

Pores that allow calcium to get inside of a cell.

cancer

A disease involving abnormal uncontrolled growth of a group of cells. Damage may be caused by local growth or spread throughout the body.

caveolar kinases

Enzymes that catalyze the transfer of phosphate groups from a high-energy phosphate-containing molecule (as ATP or ADP) to a substrate in small vesicular invaginations of the cell membrane.

cell

The basic subunit of any living organism; the simplest unit that can exist as an independent living system. There are many different types of cells in people, each with specific characteristics. The lung has more than 25 different types of cells.

chemokines

Soluble proteins produced and released by a wide variety of cell types during the initial phase of host response to injury, allergens, antigens, or invading microorganisms.

chromatin

The genetic material of the nucleus, consisting of basic proteins that are usually dispersed in the interphase and condensed into chromosomes in mitosis and meiosis.

chromosomes

The structures of a cell that contain the genes, or hereditary factors, and are constant in numbers in each species.

clone

A group of genetically identical cells or organisms asexually descended from a common ancestor. All cells in the clone have the same genetic material and are exact copies of the original. The word is also applied to a single gene. An important biotechnology tool is the ability to isolate

and make many copies of (clone) specific genes.

collagen

A key fibrous element of supporting tissue. It provides the strength to many organs.

COPD

(Chronic Obstructive Pulmonary Disease) Refers to chronic bronchitis and emphysema, common serious diseases which are characterized by irreversible obstruction to flow of air in the lungs.

corticosteroid

A drug that has actions similar to the natural cortisone of the body.

COX-2

A protein thought to play important roles in cancer development, but which has many other functions as well.

cryptococcus neoformans

A species of yeast-like fungi that causes an acute or chronic infection resulting in a pulmonary, systematic, or meningeal infection in humans.

cystic fibrosis

An inherited disease that is caused by a defect in transportation of certain salts across biologic membranes. Many organs are affected. In the lung, a severe form of bronchitis is produced in children and young adults.

cytokines

Protein chemical messengers involved in the inflammatory process, usually from white blood or similar cells.

cytoskeleton

The network of protein filaments and microtubules in the cells that controls cell shape, maintains intracellular organization, and is involved in cell movement.

cytotoxic

Toxic to cells.

dedifferentiation

Reversion of specialized structures (as cells) to a more generalized or primitive condition, often as a preliminary to major physiological or structural change.

desensitizing

To make (a sensitized or hypersensitive individual) insensitive or nonre-active to a sensitizing agent.

differentiation

The development of a discriminating conditioned response with a positive response to one stimulus and absence of the response on the application of similar but discriminably different stimuli. The maturation of cells from premature forms to specific forms such as lining cells of the airways and blood vessels.

distal

Situated away from the point of attachment or origin or a central point.

DNA

(deoxyribonucleic acid) The molecule containing hereditary information in all but the most primitive organisms. Genes and chromosomes are composed of DNA.

edema

Accumulation of excessive fluid in tissues.

elastin

A fibrous element of supporting tissue. It provides the stretchable characteristic of the lung. Destruction of elastin is thought to be the key step in the production of emphysema.

emphysema

A condition characterized by the destruction of the walls of air spaces, which results in permanently abnormally enlarged air spaces. This

condition decreases the amount of lung surface available for the uptake of oxygen. The resistance to air flow in the air passages is increased, requiring more breathing effort. Severe emphysema is characterized by a profound sense of breathlessness.

endothelial

Cells comprising the inside layer of the walls of certain hollow organs such as blood vessels.

enzymes

Proteins that speed up specific biochemical processes in an organism. They are fundamental to virtually all biochemical processes.

eosinophil

A white blood cell that contains granules filled with a specific set of chemicals and enzymes that influence inflammatory reactions. They are increased in several classes of disease, including allergic diseases.

epithelial cells

Cells lining the walls of certain organs, such as the airways of the lung.

fibroblast

An elongated, flattened cell present in connective tissue which produces fibrous tissue.

fibrosis

The formation of scar tissue; excessive formation of scar tissue throughout the lung is called "pulmonary fibrosis."

gene

A sequence of DNA in the nucleus of a cell that codes for the production of a specific protein.

gene therapy

The introduction of a foreign gene into a cell to make that cell produce a protein that it otherwise would not have produced. The form of gene therapy being studied intensively

involves provision of a gene which is lacking or not functioning properly. Very promising research is being conducted to develop gene therapy for cystic fibrosis and the hereditary form of emphysema.

gland

An organ that secretes a substance.

graft vs. host disease

A serious complication of transplantation in which donor immune cells that are transplanted recognize the body as foreign and attack the recipient's cells.

heat shock proteins

Also called stress proteins, these proteins are found in all living organisms. They play a central role in the survival of cells under stress, and are activated by heat, radiation, and chemotherapy.

HIV

(Human Immunodeficiency Virus) The agent responsible for causing AIDS. Patients with HIV infection will ordinarily develop abnormal immune systems and are predisposed to infection with organisms such as *Pneumocystis carinii* and *Mycobacterium tuberculosis*.

hyperoxia

The use of high concentrations of oxygen. Hyperoxia is commonly used as lifesaving therapy in patients with profound loss of lung function, but prolonged use of hyperoxia can lead to inflammation, fluid accumulation, lung failure, and even death.

hypoxia

A pathological condition in which the body as a whole (generalized hypoxia), or region of the body (tissue hypoxia), or the blood is deprived of adequate oxygen supply.

idiopathic pulmonary fibrosis (IPF)

A chronic and usually progressive lung disorder of unknown cause.

immunization

A medical treatment that imparts immunity to a specific disease. “Vaccinations” and “flu shots” are immunizations.

immunodulation

Changing certain characteristics of the immune system, which may be done as therapy for a disease state.

inflammation

A fundamental response to injury or abnormal stimulation, consisting of complex reactions occurring in the affected blood vessels and adjacent tissues. The inflammatory process includes destruction or removal of the material causing the injury and responses that lead to repair and healing, or responses that lead to a variety of acute and chronic disease states.

interstitial

The supporting matrix of the lungs, as opposed to the airways or air sacs. May be the site of specific diseases.

in vitro

Outside of the living body; in a test tube or glass.

in vivo

Inside of the living body of a plant or animal; opposite of *in vitro*. Scientific studies frequently involve testing concepts in both ways.

leukocyte

A white blood cell that constitutes a major component of the immune system.

lipids

A general term for molecules that are the building blocks of fats.

lipoprotein

A molecule made of a lipid and a protein.

macrophage

Specialized cells that engulf and destroy bacteria and foreign particles in the lungs and other organs. In the lungs, these cells are called *alveolar macrophages*.

malignant

Usually refers to the behavior of a tumor which is invasive, destructive, or spreads to other parts of the body.

membrane

The surface covering a biologic entity. Example: mucous membranes line the nose and airways.

metabolism

The chemical processes of the body.

metastasis

The spreading of a disease to another part of the body.

molecular biology

A field of biology dealing with the fundamental biochemical organization of living matter, especially the biochemical basis for inheritance. For example, molecular biologists may study genes, DNA, or protein synthesis.

molecule

The smallest amount of a specific chemical substance that can exist alone.

mutation

Any alteration in the base sequence along the DNA, changing the genetic material.

myofibroblasts

Connective tissue cells that are important in normal wound-repair responses. They also play an important role in the development of the air sacs in the lungs, called alveoli.

neutrophil

A white blood cell important in the immune process.

oxidants

Molecules that react readily with other molecules in a manner similar to the way in which oxygen reacts. The reaction can be destructive, and the generation of an excess of powerful oxidants is thought to play a role in several disease processes in the lung.

peptide

A sequence of amino acids. Peptides are combined to make proteins.

phospholipid

A form of lipid that is combined with the phosphorous molecule. Phospholipids are key elements in the surfactant of the lung, which prevents alveoli from collapsing.

physiology

The science of living things, dealing with the normal life process.

pneumonia

Inflammation of the alveoli and/or the supporting structures of the lung (air sacs). Can be due to infection by bacteria, viruses, fungi, or other microorganisms. Some pneumonias are not infectious.

pneumocystis carinii

A microorganism now considered to be a fungus that is an important cause of pneumonia in AIDS and other immune-suppressed patients.

prostaglandin

A family of fatty acid derivatives producing a variety of biological effects, including inflammatory responses. Tiny amounts have potent effects.

proteins

Organic compounds made up of amino acids; proteins are one of the major constituents of plant and animal cells.

pulmonary arteries

The arteries that bring oxygen-poor blood to the lung from the heart.

pulmonary edema

Excess fluid in the lungs.

pulmonary fibrosis

A condition characterized by diffuse scar formation in the supporting structure of the lung.

pulmonary hypertension

Abnormally high blood pressure in the arteries of the lungs.

RDS

Respiratory distress syndrome occurs in premature infants as a result of a lack of adequate surfactant, which makes the air sacs difficult to expand.

receptor

In nerves, a specialized nerve ending able to receive and respond to a stimulus in a specific way. Also used to describe the molecule on a cell surface that interacts with a specific chemical messenger.

sarcoidosis

A disease that involves a distinct form of diffuse inflammation of the lungs, lymph nodes, and other organs. It is prevalent in African-Americans and may lead to pulmonary fibrosis.

sepsis

The presence of various pus-forming and other pathogenic microorganisms, or their toxins, in the blood.

SIDS

(sudden infant death syndrome) The unexplained and sudden death of an infant, one month to one year of age.

sleep apnea

One of several common respiratory disorders of adults and children, characterized by periodic cessation of breathing during sleep. It is usually accompanied by loud snoring and results in daytime sleepiness and other severe disabling characteristics.

streptococcus

A form of bacteria that may cause pneumonia.

surfactant

A surface-tension lowering agent. Pulmonary surfactant is produced by alveolar type II cells, which line the alveolar space. It is essential for normal expansion of the lungs and is abnormal or lacking in premature infants with respiratory distress syndrome and other diseases.

syndrome

A specific set of symptoms and/or medical findings that often occur together but are not distinct enough to be thought of as a single disease entity, e.g., sleep apnea syndrome.

theory

General principles derived from a body of scientific data to explain a natural occurrence.

toxicity

Ability to cause harm.

tuberculosis

An infectious disease due to a microorganism called *Mycobacterium tuberculosis*. The disease usually begins in the lung, but can involve virtually any part of the body. Progression from infection to disease is more likely in patients with an abnormal immune system.

tumor

An abnormal collection of cells into a distinct physical entity.

t-cells

Small white blood cells that orchestrate and/or directly participate in the immune defenses; also known as T-lymphocytes, they are processed in the thymus and secrete lymphokines.

type I cells

The cells that line the alveoli that produce surfactant.

vaccine

An inactivated (noninfectious) preparation of a microorganism that can be injected into a patient to stimulate the production of antibodies in order to protect the patient from infection by the live organism. Also an active but attenuated microorganism which causes a mild form of the disease while stimulating antibody production.

ventilator

A device that provides for mechanically assisted breathing.

virus

A tiny infectious agent that requires a host cell in order to replicate. It is composed of either RNA or DNA wrapped in a protein coat. Viruses cause a wide variety of diseases.

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